*Synovial Fluid Changes in Joint Disease*

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# *Synovial Fluid Changes in Joint Disease*

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## *Preface*

THE studies on synovial fluid reported in this volume were initiated twenty years ago in the hope that knowledge of the changes in the fluid in joint disease would aid in better understanding and differential diagnosis of the various arthritides This project has been part of a larger program, the aim of which has been to care for patients with joint disease and to gain knowledge of the anatomy and physiology of articular structures, the diseases which affect them and the individuals so afflicted This program, which has been carried out by the Arthritis Group at the Massachusetts General Hospital, has been supported by the Robert W Lovett Memorial Foundation for the Study of Crippling Disease, Harvard Medical School since its inception, and by the Commonwealth Fund and the Massachusetts Department of Public Health subsequently

From the outset it was apparent that study of the origin and properties of normal synovial fluid was essential as a basis for comparison and evaluation of the changes produced by disease Normal fluid was obtained post mortem from patients who had had no signs or symptoms of joint disease Because sufficient fluid for complete analysis cannot be aspirated from normal human joints fluid was also obtained from normal cattle immediately after slaughter In addition to the acquisition of knowledge of the characteristics of normal synovial fluid, studies were undertaken to add to the existing information concerning the exchange of substances across the blood-joint barrier

Fluids from pathological effusions were obtained from the large group of patients with joint disease seen by the Lovett Foundation Group on the wards and in the clinics of the Massachusetts

General Hospital The alterations in the characteristics of the fluid with disease were found to reflect the degree of change in the synovial tissues and to be of value in diagnosis or to aid in interpreting alterations in the permeability of the blood joint barrier and in intra-articular metabolism On the basis of the findings in the first 800 fluids it became apparent that pathological effusions could be divided into two major groups the first, Group I, which contains fluids with relatively slight abnormalities, was found to include diseases in which the inflammation was trau matic in origin, whereas the second, Group II, includes rheuma toid arthritis and infectious arthritis

In this volume the present concept of the nature of synovial fluid and the characteristics of normal fluid will be presented first The findings in respect to each individual characteristic of joint fluid under conditions of disease will then be described and related, when possible, to the underlying physiological alterations The abnormalities found in fluids from the various types of joint disease and their diagnostic significance will be discussed

It is only by studies of this type that one can learn more of the physiological and metabolic alterations in articular tissues in joint disease and obtain clues as to the pathogenic mechanisms involved In diseases, such as rheumatoid arthritis, in which the etiology and pathogenicity are unknown, elucidation of under lying mechanisms becomes of major importance

The solution of many of these problems must await the acquisition of basic chemical knowledge This is well exemplified in the case of mucin In this instance we are in need of information concerning the chemical composition of the polysaccharides of connective tissue, their structural configuration, the enzyme sys tems concerned with their synthesis and degradation and the intermediate compounds As this knowledge comes to hand the metabolism of mucin in articular diseases can be investigated again The results obtained by new methods should reveal dif ferences in articular disease in terms of cellular derangements and enzymatic systems It is hoped that the alterations observed can be translated in terms of disease mechanism Such an ap proach to the study of chronic rheumatic diseases is enhanced by constant interplay between a group of workers trained in various disciplines

The solution of many of the problems that arise at the bedside lies in the laboratory Likewise the validity of a given hypothesis which has its origin in the laboratory can only be tested in terms of disease significance at the bedside It is this crossing and re crossing from ward to laboratory which is so vital to our primary objectives, namely the amelioration, alleviation and prevention of the ravages of a group of chronic disabling diseases Achievement of these goals, be it partial or complete, can come only from a better understanding of the course and nature of the underlying disease mechanisms and the testing of possible means of arrest and prevention

We are indebted to Dr Howard C Coggeshall for the initial cytological studies, including the use of the supravital technique, and for his assistance in the study of the initial case material We also are indebted to Dr J Peter Kulka for the review and description of the pathological material and to Dr G E Perlmann for the reported electrophoretic studies which were carried out under her supervision We wish to thank all past and present members of the Lovett Foundation Group who have given generously of time and thought and furnished us with case material It would have been impossible to accumulate the mass of data if it had not been for the assistance of the following, to whom we also wish to acknowledge our debt Miss Elsie C Rossmeisl, Mrs R Barbara Peabody, Miss Elizabeth Manning, Mrs Dorothy Slobodkin, Miss Olivia B Swaim, Miss Barbara Kraft and Miss Katherine L Brine We wish to express our appreciation to Miss Hope Richardson for bibliographic and editorial assistance and to Mrs Magdalene Evers for secretarial assistance in preparation of the manuscript

M W R
W B

*November 1952*

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# I

## *Introduction*

PARACELSUS (1493-1541) is credited with having first noted the presence of viscous fluid in the articular cavities.[146] The fluid is contained in the space formed by the opposing cartilage covered epiphyses and the connecting joint capsule. It is now generally agreed that the highly vascular synovial tissue lining the capsule is slightly modified connective tissue, varying in different parts of the joint as described by Key,[108] and not an actual membrane. Many recent workers consider the articular cavities as connective tissue spaces, synovial fluid as tissue fluid and the embodied mucin as the equivalent of the polysaccharide protein component of other connective tissue (see reviews[1, 79]). The contents of the articular cavity are presumably in direct communication with the intercellular fluid of the synovialis. From available data, it has been concluded that synovial fluid is a protein containing dialysate of blood plasma to which mucin, secreted by the synovial cells, is added as the plasma water diffuses through the synovial tissue spaces into the larger tissue space, the joint cavity.[12]

Synovial fluid, as might be expected from the hypothesis that it is tissue fluid, shows changes with disease which reflect alterations in the synovial tissues and intra articular metabolism. The normal exchange of substances between the vascular and lymphatic systems may be disturbed or there may be altered utilization, formation or destruction of various constituents within the joint. Examination of synovial fluid should therefore yield information concerning the type and degree of change in the joint.

Analysis of fluid has, however, been of limited value in the diagnosis and prognosis of joint disorders. The knowledge of the

physical and chemical characteristics of normal synovial fluid that is necessary to make sound evaluation of pathological fluids has accumulated slowly Furthermore, although a few studies on small groups of fluids from various joint diseases have been reported, no extensive investigations have been carried out, so information on the variations in the fluid under conditions of disease has been lacking The present study, in which the findings in 1,500 fluids from various diseases are compared with the normal and, insofar as possible, interpreted in terms of the underlying pathological physiological changes, indicates the value of joint aspiration

## NORMAL SYNOVIAL FLUID

The following summary of the characteristics of normal synovial fluid is accompanied by a discussion of the exchange of substances through normal synovial tissues, a process which must be understood in order to evaluate the altered permeability produced by disease The details of the studies leading to the conclusions outlined in this chapter have previously been reported[1-, 38, 167, 171] Normal human synovial fluid was obtained post mortem from patients who had had no signs or symptoms of joint disease Because sufficient fluid for complete analysis cannot be aspirated from normal human joints, many of the data were obtained from cattle fluid, which is apparently, essentially the same as human

Normal human synovial fluid is a clear, pale yellow, viscous fluid which does not clot As might be expected in a fluid that serves chiefly for nourishment of avascular cartilage and for lubrication, it contains very few cells The cytology is comparable to that of other tissue fluids substantiating the concept of the joint cavity as a connective tissue space The amount of fluid obtainable from a normal human joint varies from 0 13 to 3 5 cc (Table I) The volume of fluid present is determined normally by two opposing forces capillary pressure on one hand, and the difference in osmotic pressure between plasma and fluid on the other The slightly negative intra articular pressure, which varies with motion, also appears to play a role in this equilibrium Ekholm and Norback[6-4] found an increase in the volume of fluid in rabbits joints after exercise

TABLE I Normal Human Synovial Fluid

| | Range | Average |
|---|---|---|
| Amount per knee joint, cc. | 0 13 –3 5 | 1 1 |
| Relative viscosity at 25 C | 5 7 – 1160 | 235 |
| pH | 7.29 –7 45 | 7 39 |
| Total cell count, cells per cu mm | 13 – 180 | 63 |
| Differential–per cent | | |
| Polymorphonuclears | 0 – 25 | 6.5 |
| Lymphocytes | 0 – 78 | 24 6 |
| Monocytes | 0 – 71 | 47 9 |
| Clasmatocytes | 0 – 26 | 10 1 |
| Unclassified phagocytes | 0 – 21 | 4 9 |
| Synovial cells | 0 – 12 | 4 3 |
| Total solids gm. per 100 gm | 2 40 –4 83 | 3 41 |
| Total albumin and globulin gm per 100 cc. | 1 07 –2 13 | 1 72 |
| Albumin gm per 100 cc | | 1 02* |
| Globulin gm per 100 cc | | 05* |
| Mucin nitrogen gm per 100 cc. | 0 068–0 135 | 0 104 |
| Mucin glucosamine gm per 100 cc | 0 012–0 132 | 0 074 |
| Fibrinogen | 0 | 0 |
| Glucose | Approximately same concentration as in plasma | |
| Non protein nitrogen† | Approximately same concentration as in plasma | |
| Electrolytes† | Approximately same concentration as in plasma dialysate | |

*Analysis has been made on only 1 fluid from a patient without edema. The averages for total albumin and globulin include 9 other fluids
†See Table II

Substances entering the joint must pass the capillary endothelium and diffuse through the intercellular spaces of the synovialis Comparison of the composition of joint fluid with that of plasma indicates that non electrolytes diffuse readily in either direction between blood and synovial fluid and that electrolytes are distributed in accord with the Gibbs Donnan theory of membrane equilibrium[167] (Table II) The concentration of nonelectrolytes (glucose, non protein nitrogen, uric acid) is approximately equal in fluid and serum Chloride and bicarbonate are present in higher concentration in the fluid than in the serum while the concentrations of sodium potassium, calcium and magnesium are lower in the fluid The low distribution ratios obtained for potassium, calcium and magnesium indicate that part of each of these cations is held in the serum, presumably bound to protein It is of interest that Joseph, Reed, Steck, Folk and Kaplan[102] found the mobility of many ions in synovial tissues the same as in water but that the bivalent cations had lower apparent mobilities in the tissues than in water Thus the distribution of electro-

lytes and non electrolytes between serum and fluid is in accord with the concept that synovial fluid is a dialysate in equilibrium with blood plasma This relationship is also suggested by the marked vascularity of the synovial intima whose numerous capillaries and venules are *in close proximity to the articular lumen*[12, 79] (See Figures 1 and 2 ) Such a theory explains all that is known of the physical and chemical composition of synovial fluid except the presence of albumin, globulin and mucin Slight capillary permeability to protein presumably explains the entrance of albumin and globulin into the joint cavity The high albumin/globulin ratio of the fluid compared with that of the serum, which accords with the findings of other investigators in lymph, edema and ascitic fluids (see review[12]), indicates greater permeability to albumin than to globulin, corresponding to the difference in molecular weights The presence of mucin, whether it be formed by the surrounding connective tissue, as is most likely,[17, 33, 93, 99, 107, 110, 201] or by cartilage, in no way invalidates the theory The properties which distinguish synovial fluid from other fluids which are also dialysates of blood plasma are attributable to mucin

Mucin, the characteristic component of synovial fluid, is an easily dissociable protein-polysaccharide complex The exact nature of the components has not been determined It is known however, that the polysaccharide contains equimolar amounts of acetyl glucosamine and a uronic acid[132] and that the protein component consists of at least an albumin and several globulin fractions[170] Jeanloz[96] has shown that the polysaccharide is a *non ramified polymer of D glucuronic acid and N acetyl D glucosamine* residues connected through $\beta$ 1-3 linkages Glucosamine constitutes 40 per cent of the polysaccharide and 8 per cent of the mucin[167] The degree of dissociation of the protein polysaccharide complex in vivo has not been determined with certainty [12, 65, 79, 131, 139, 170]

The hypothesis that mucin is formed by the cells of the connective tissue surrounding the joint is supported by good evidence[14, 69, 118b, 131] A substance similar to synovial fluid mucin has been found in the subcutaneous tissues of rabbits[164] the sexual skin of monkeys[138] cocks combs[83] and the connective tissue lining the astragalotibial joints of cattle[164] In addition the en

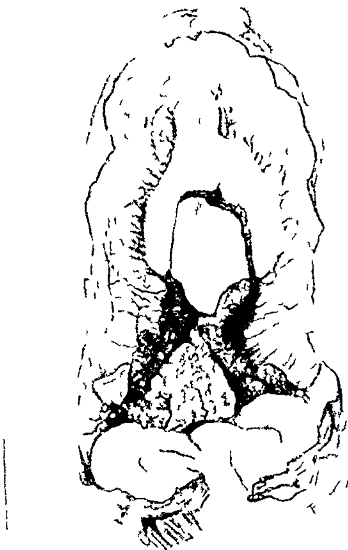


FIGURE 1 A natural sized drawing of the interior of the left knee joint of a normal dog

The blood vessels of the rear extremities had been perfused with a suspension of graphite It will be noted that the subsynovial tissues are very vascular particularly in the region of the infrapatellar fat pad and immediately adjacent to the patella

TABLE II Comparison of the Distribution Ratios for Synovial Fluid, Edema Fluid the "In Vivo" Dialysate Ascitic Fluid, and Lymph and the Theoretical Donnan Ratios (See Review[11])

| | Synovial fluid Cattle | Synovial fluid Human | Edema fluid | "In vivo dialysate" dog | Ascitic fluid | Lymph |
|---|---|---|---|---|---|---|
| $\frac{Cl}{Cl_f}$ | 99 | 98 | 97 | 98 | 98 | 95 |
| $\frac{HCO_3}{HCO_{3f}}$ | 94 | | 96 | 97 | 97 | |
| $\frac{PO_4}{PO_{4f}}$ | 1 00 | | 1 03 | 1 17 | 1 12 | 1 07 |
| $\frac{Na_f}{Na}$ | 93 | | 97 | 91 | 94 | |
| $\frac{K_f}{K}$ | 75 | | 73 | 78 | 94 | |
| $\sqrt{\frac{Ca_f}{Ca}}$ | 83 | 87 | 80 | 76 | 84 | |
| $\sqrt{\frac{Mg_f}{Mg}}$ | 88 | | | 66 | 86 | |
| Theoretical Donnan | 93 | 93 | 96 | 93 | 97 | |
| $\frac{NPN_f}{NPN}$ | 87 | 91 | | | | |
| $\frac{\text{Uric acid}_f}{\text{Uric acid}}$ | 84 | | | | | |

largement of the Golgi apparatus of the synovial cells in response to trauma[37, 110] and the associated accumulation of intercellular mucoid material demonstrated by King[110] offer support for this theory

The mode of destruction of mucin is not known but in view of the difficulty with which large molecules leave the joint cavity[13] it is probable that breakdown occurs in the synovial fluid or tissues Many bacterial and tissue enzymes that produce in vitro degradation of mucin have been recognized but similar enzymatic activity has not been demonstrated in synovial fluid or tissues[131, 170] Ascorbic acid, which also causes degradation of mucin in vitro, has not been shown to have hyaluronidase activity in vivo Testicular extract, however has been found to maintain



FIGURE 2 Camera lucida drawing of low magnification (x100) of a microscopic section taken from the right knee joint of the same dog as in *Figure 1*

The rich subsynovial vascular system is well illustrated In some instances the blood capillaries are separated from the interior of the joint by not more than one or two layers of synovial lining cells

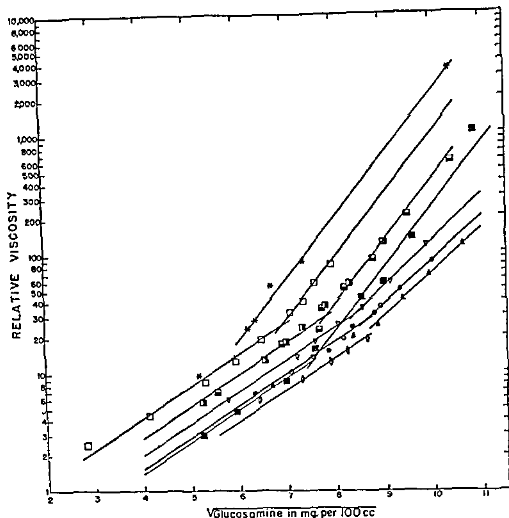



FIGURE 3 Relationship between the log of the viscosity and the square root of the concentration of mucin glucosamine in synovial fluid and in mucin and polysaccharide solutions Viscosity measurements were made at 38 C

- * Bursal fluid (human) in 0 9 per cent NaCl
- □ Normal carpometacarpal and astragalotibial joint fluid (cattle)
- ◨ Mucin (cattle) in M/15 Na HPO₄
- ⊟ Mucin (cattle) in 0 5 per cent NaHCO
- ■ Mucin (cattle) in joint fluid (cattle)
- ▿ Mucin (cattle) in 0 5 per cent $Na_2CO_3$
- ∘ Astragalotibial joint fluid (cattle) in 0 9 per cent NaCl
- • Mucin (cattle) in serum (human) diluted with Ringer s phosphate solution
- ▴ Mucin (cattle) in M/15 Na acetate
- ◊ Polysaccharide (cattle) in 0 9 per cent NaCl

Figure 3 originally printed in Ropes M W Robertson W v B Rossmeisl E C Peabody R B and Bauer W Synovial Fluid Mucin Acta Med Scandinav 1947 Suppl 196 700

its hyaluronidase activity when injected into joints of patients having rheumatoid arthritis[156] Exposure of synovial fluid or hyaluronic acid solutions to X rays in vitro has been shown to cause marked reduction of viscosity[157]

The high viscosity of normal synovial fluid is due to the presence of mucin[44, 131, 170] This is shown by the fact that the viscosity of the fluid approaches that of water after the mucin is precipitated or destroyed enzymatically Evidence that the long chain molecule of the polysaccharide component causes the viscosity is given by the persistence of the viscosity of mucin solutions after tryptic digestion of the proteins Gunter[80] noted similar persistence of the fiber-forming capacity of cattle synovial fluid after tryptic digestion

A proportional relationship has been found to exist between the log of the viscosity of a mucin or polysaccharide solution or synovial fluid and the square root of the mucin glucosamine concentration[170] (Figure 3) This proportionality, which apparently remains constant even after partial splitting of the polysaccharide, provides a possible means of estimating the degree of degradation of mucin in pathological effusions The most reliable indication of the state of mucin in any fluid, however, is the nature of the precipitate obtained with acetic acid Further evidence of the state of mucin may be obtained in some cases by the nitrogen/glucosamine ratio (a comparison of the methods is given on p 62)

The properties of mucin suggest its participation in various physiological processes It is presumably of great importance in the lubrication of joints[79, 97, 170] Because of its high base binding power it apparently aids in regulation of calcium equilibrium[47, 167] It also affects the transfer of water between plasma and synovial fluid[167] Its effect in holding water in the intercellular tissue spaces is suggested particularly in myxedema, a disease in which the amount of mucin in synovial and other connective tissues is greatly increased[7a, 8, 14, 205a, 213]

The permeability of the synovial tissues to substances of large molecular size such as proteins is of special significance in the physiology of joints because of the effect of such substances on osmotic pressure and thereby on water exchange Possibly it also explains the frequent localization of disease processes in the

Absorption is greatly increased from joints which are exercised and from those in which severe, acute inflammation has been produced, and is decreased with chronic inflammation of joints[51, 61, 106, 115, 185, 186] Efskind,[61] however, found reduced absorption of perabrodil and indigo carmine in hemorrhagic traumatic arthritis as well as rheumatoid arthritis Edlund[59] ascribed the increased absorption after exercise to a "breaking of the resistance of the tissues and concluded that the mechanism of absorption was the same in synovial tissues as in that described for other connective tissues by McMaster (see review[79])

Edlund and Linderholm[60] noted increased absorption of water and hemoglobin after administration of salyrgan and a decrease following production of subcutaneous inflammation or contralateral intra articular burns[60] Hoffheinz[87] concluded that blocking or cutting the nerve supply to a joint decreased absorption of sodium iodide from the joint Seifter, Baeder and Begamy[181] reported that hyaluronidase and desoxycorticosterone acetate increased absorption of phenolsulfonphthalein from joints Cortisone and 21 acetoxypregnenolone decreased the absorption from joints and counteracted the increase produced by hyaluronidase[182] Edlund,[59] however, concluded that desoxycorticosterone acetate does not affect absorption from normal joints but decreases absorption from mildly injured joints and increases it from severely injured joints

The only experimental evidence of the presence of immune bodies in normal synovial fluid is found in the work of Poehlmann[152] He studied 100 fluids from patients having various stages of syphilis with and without joint symptoms Of the patients with positive blood Wassermann reactions, 25 of 36 untreated secondary cases, 2 of 12 latent cases, and 3 of 9 tertiary cases had positive reactions in the fluid He never found a positive Wassermann in the fluid when the reaction in the blood was negative

Relatively little is known of the enzymes of normal synovial fluid Podkaminsky[151] noted the presence of an amylase, protease and lipase but no catalase We have found, however, that normal fluid (bovine and human) causes breakdown of hydrogen peroxide The activity of alkaline phosphatase in normal cattle fluid is higher than that in the serum but varies markedly from fluid to

articulations Compared with true membranes, synovial tissue has a markedly greater permeability [12]

The factors affecting permeability are only partially under stood Engel[64] has concluded, from the results of experiments in animals on which unilateral lumbosacral sympathectomy had been performed that loss of activity of the sympathetic system decreases capillary permeability Cheng [35] however, has been unable to corroborate Engels findings In a comparison of acid and alkaline dyes, Tani[200] found that 36 of 50 acid dyes and 16 of 26 basic dyes entered the joint Engel,[63] however, noted that almost all acid dyes but no alkaline dyes appeared in the joint perfusate He explained the difference by the hypothesis that the lipoid soluble alkaline dyes were removed from the blood stream by the cells and tissues within a few minutes, whereas the acid dyes remained in the blood for hours

Permeability has been found to be increased in inflamed joints by von Seemen [203] Burman and Kling,[27] and Bondi and Jacoby,[21] although Engel[63] found decreased permeability to acid dyes and Scott Thoburn and Hanzlik[178] and Frohlich and Singer[78] noted no increased entrance of salicylates into inflamed joints Tani[200] reported greater entrance of both acid and alkaline dyes in in flammation of short duration but a decrease after 11 to 14 days

The entrance of particulate matter into the joint has been less thoroughly investigated Kuhns and Weatherford[118] found that carbon particles injected into the abdominal wall of rats appeared in the histiocytes of the synovial membrane but in smaller quantities than in the liver spleen, kidney and bone marrow Experimental studies have shown that living bacteria gain access to synovial fluid more readily than to spinal fluid, aqueous humor or urine (see review[12])

Resorption of small molecules takes place almost entirely by way of the subsynovial blood capillaries and only to a slight degree through the lymphatics [12, 79] Proteins in contrast to small, readily diffusible substances are removed from joints only by way of the lymphatics [12] The removal of particulate matter in cluding the cellular debris of wear and tear, is slower and is achieved by a combination of several processes in which the mononuclear phagocytes, the predominant cellular constituents of synovial fluid, play the chief role [12, 79]

substances as sugar to be established between serum and fluid In some cases the patients were not fasting or were under anesthesia at the time of aspiration The concentrations of sugar and phosphate in such cases were not of value for comparison with the findings in other fluids

The skin over the joint to be aspirated was prepared by shaving and washing with green soap, alcohol and ether 12 hours before aspiration and again washing with iodine and alcohol at the time of aspiration The skin and the subcutaneous and subsynovial tissues were infiltrated with novocaine at the site of puncture

The majority of fluids were obtained from knees, although in a few cases, shoulder, elbow, hip or ankle joints were aspirated On the rare occasions when fluid was aspirated simultaneously from one or both knees and another joint, it was similar in all

The usual site of puncture in the knee was slightly above and approximately 2 cm lateral to the patella From this position one could enter readily either the quadriceps pouch or the region of the joint cavity under the patella An 18 or 19 gauge needle with stylet, of the type employed for lumbar puncture, was used for withdrawing the fluid Intra articular pressure was determined by means of an Ayer manometer In order to obtain comparable and consistent pressure readings, the patients were recumbent and quiet, with the leg extended in a position of comfort If any motion of the leg occurred while the pressure was being determined, a rise in pressure, which subsided slowly to the original level, resulted In order to facilitate the passage of extremely viscous fluids into the manometer, it was often necessary to rotate the manometer so that it was parallel to the leg and therefore level with the joint After rotating the manometer back to its normal position, readings were not made until the fluid level had been constant for several minutes Blood was obtained from the median cubital vein at the time of aspiration Following aspiration an elastic bandage was applied and the patient allowed to walk immediately if necessary

*Examination of Fluid*

The first sample of fluid was collected for bacteriological studies in a sterile tube, usually containing 2 to 3 mg of sodium citrate per cc of fluid In the sample used for cytological studies and

fluid[167] The activity in normal human fluid is much lower than that in the serum

### SYNOVIAL FLUID IN PATIENTS WITH EDEMA

The synovial fluid from patients with edema but no joint disease provides additional evidence in support of the hypothesis that synovial fluid is a plasma dialysate to which mucin is added as the plasma water diffuses through the synovialis This synovial fluid is comparable to the edema fluid obtained from other con nective tissues A disturbance of the equilibrium regulating the formation of tissue fluid, which is usually due to increased capillary hydrostatic pressure and/or decreased osmotic pressure difference between plasma and fluid, accounts for the increased volume of fluid in both cases All the findings in the synovia in such patients indicate dilution of normal fluid

In the series studied in this laboratory, the amount obtained from the knee was occasionally as much as 40 cc[171] It was clear, very pale yellow and much less viscous than normal with an average relative viscosity of 53 in contrast to 235 Ragan[155] in 5 fluids found volumes from 12 to 30 cc with viscosities ranging from 3 to 62 2 The total nucleated cell count also was lower than normal, ranging from 0 to 128[38 119 1 8] The specific gravity varied from 1 008 to 1 015[90 171] The average content of total solids was reduced from 3 41 gm per 100 gm to 2 23 The pH remained essentially normal, with a range from 7 29 to 7 45[23 171] The average total protein, exclusive of mucin was 0 63 gm per 100 cc in contrast to 1 72 gm in fluid from patients without edema The globulin fraction was very low, ranging from 0 to 0 33 gm per 100 cc[31 171] The average concentration of mucin nitrogen in our series was reduced from the normal value of 0 104 gm nitrogen per 100 cc to 0 061 gm[171] The lowered mucin content associated with the increased diffusion of water into joints in patients with edema suggests that the rate of formation of mucin is not so accelerated as the rate of transudation of water

### METHODS

*Aspiration of Fluid*

The majority of the patients fasted for at least 12 hours before the joints were aspirated in order to allow equilibrium for such

plain infusion broth or thioglycollate broth were adequate For gonococci, meningococci, *Streptobacillus moniliformis* or pleuro pneumonia like organisms, boiled blood ascitic agar plates or broth were used For bacteroides, thioglycollate broth was used and cultures were kept 2 weeks The percentage of positive results in infectious arthritis was increased if the cultures were planted at the bedside They were incubated at 37° C aerobically and under 10 per cent $CO_2$ In most cases, cultures were made also in anaerobic meat tubes All cultures were kept for 4 days and many for 2 weeks Smears stained with Gram's stain were examined in all cases in which cultures were made Some of the fluids from rheumatoid arthritis were inoculated into chick embryos, and were injected into mice intravenously, intra articularly or intracerebrally Guinea pig inoculation was necessary in tuberculous arthritis In a few cases, cultures for acid fast bacilli were made on Dubos s medium [56, 70]

*Cytology* Cytological methods were essentially the same as those used in the study of normal human fluid [38] The erythrocytes and leukocytes were counted simultaneously in a standard hemocytometer In all cases except occasional traumatic effusions, it was necessary to dilute the fluid in a standard white cell counting pipette Normal saline was used, since the routine diluents cause precipitation of mucin with resultant reduction in the number of cells in the supernatant fluid Addition of methylene blue to the saline aided in recognition of nucleated cells

Differential counts were made either on thin fixed smears stained with Wright s stain or on fresh preparations stained supravitally with neutral red and Janus green [11, 205] In many cases counts were obtained by both methods and showed essentially the same percentage of cell types The chief differences appeared in the distribution of mononuclear cells, which at times are relatively hard to differentiate with Wright s stain in fixed smears However, differentiation of one mononuclear cell from another is not absolutely essential for diagnostic purposes The relative proportion of polymorphonuclear to mononuclear cells gives the best indication of the degree and type of inflammation in the synovial tissues The total number of phagocytes is of course, of additional value in determining the degree of tissue irritation and injury In general differential counts on pathological effusions can be made

determination of fibrinogen content, clotting was prevented by the addition of 2 mg of potassium oxalate per cc of fluid For the other analyses, no anticoagulant was added The specimens of fluid and blood to be used for determination of pH were collected under oil

The determinations which were made in each case depended on the amount of fluid obtained A few drops were sufficient for determination of the gross appearance, total nucleated cell count differential count, viscosity and the type of mucin precipitate The total amount necessary for the other most significant analyses —determinations of the sugar, total protein, globulin and mucin concentrations pH, bacterial and immunological examinations— was at least 8 cc * In the first 400 pathological effusions examined much more complete studies were made, including other non electrolytes (non protein nitrogen and uric acid) and electrolytes (calcium, phosphate and chloride) Since no diagnostic or prognostic significance of these determinations was apparent, we do not consider them of value in the routine analysis of synovial fluid

Blood withdrawn at the time of joint aspiration, was always examined for sugar if possible and for protein fractions when indicated

*Gross appearance* The appearance of the fluid in respect to degree of turbidity, color apparent viscosity and the presence *or absence of clotting was noted at the time of withdrawal If the* fluid contained blood, it was important to determine whether it was due to a bloody tap Unequal distribution of blood between the samples, streaking of blood through any sample and rapid clotting especially if localized to the bloody streaks indicated that the bleeding was caused by the tap The presence of xanthrochromic blood pigment in the supernatant fluid after centrifuging indicated that bleeding had occurred in the joint before aspiration

*Bacteriology* Cultures were made on the majority of fluids In searching for such organisms as streptococci, staphylococci pneumococci, or *E coli* routine cultures on blood agar plates and

*Observation of the color viscosity and turbidity of the fluid its tendency to clot the type and size of the mucin precipitate formed by the addition of acetic acid to a final concentration of 1 per cent and determination of the total and differential leukocyte counts will often be of diagnostic value if facilities are not available for chemical analyses

THE CELLS OF NORMAL SYNOVIAL FLUID

| | WRIGHT'S | SUPRAVITAL |
|---|---|---|
| POLYMORPHONUCLEAR LEUKOCYTE | | |
| MONOCYTE | | |
| CLASMATOCYTE | | |
| LYMPHOCYTE | | |
| SYNOVIAL CELL | | |
| ERYTHROCYTE | | |

FIGURE 4 The appearance of the cells of normal synovial fluid with two methods of staining

satisfactorily on fixed smears Supravital preparations give somewhat more accurate results in classification of cell types but have the disadvantages of being slightly more time-consuming and of requiring that the fluid be kept warm and be examined within an hour after aspiration In fixed smears the precipitated mucin of the fluid will stain lightly (usually it is basophilic), forming an amorphous background which does not interfere with differentiation of the cells

The types of cells found in synovial fluids and their appearance with the two methods of staining are shown in Figure 4 In many pathological fluids the polymorphonuclear leukocytes, the monocytes and the clasmatocytes show signs of marked irritation with vacuolization of the cytoplasm Occasionally degenerated polymorphonuclear cells with single pyknotic nuclei or with extruding nuclei are seen.

*Physical and chemical data* The following chemical methods were used chloride, Eisenman modification of the Van Slyke method,[62] inorganic phosphate, Fiske and Subbarow [69] sodium, Rourke modification of the Kramer-Gittleman method [173] calcium Fiske and Logan [63] non protein nitrogen, Folin and Wu,[73] uric acid, either Benedict and Behre[16] or Folin,[72] sugar, Folin,[71] fatty acids Stoddard and Drury,[193] cholesterol, Bloor,[20] lactic acid, Barker and Summerson.[10] The pH was determined by means of a McInnis glass electrode, measurements being made at 25° to 28° C and corrected to 37° by the use of temperature coefficients ($\Delta$ pH/$\Delta$t = 0 006 for synovial fluid, 0 012 for serum) Specific gravity was determined in specific gravity bottles with open capillary outlets of the type described by Moore and Van Slyke [134] Total solids were obtained by drying a weighed sample of approximately 1 gm at 100° C for 48 hours Viscosity was determined either by a Hess viscosimeter or by an Ostwald viscosity pipette in a constant temperature bath Glucosamine was determined by a slight modification of the Palmer Smyth and Meyer method,[144] with the use in some cases of an Evelyn photoelectric colorimeter with filter no 520 and in other cases of a Coleman spectrophotometer Protein other than mucin was calculated from the total nitrogen (obtained by a macro- or micro-Kjeldahl method) The difference between the total nitrogen and the sum of the nonprotein and mucin nitrogen was multiplied by the factor 6.25

tissues In such cases it may prevent relaxation of tissues and hasten recovery One gets the impression, in occasional mild and moderately severe cases of rheumatoid arthritis in which effusions persist after definite general improvement, that aspiration hastens the subsidence of the effusions Aspiration of the knee effusions in long standing cases of chronic rheumatoid arthritis is sometimes indicated to allow better position and motion of the joints, to prevent further stretching and lessen relaxation of supporting structures and to improve the circulation of the synovial tissues

Although antibiotics or sulfonamides are rapidly effective in the treatment of many cases of infectious arthritis, daily joint aspirations are valuable adjuncts They are of fundamental importance in infections not susceptible of specific therapy In such cases, repeated daily aspirations with or without saline irrigations are often sufficient for cure, with resulting normal joints Open drainage with the likelihood of residual joint damage may thereby be avoided The total nucleated cell count, percentage of polymorphonuclears and sugar concentration in the fluids withdrawn daily from septic joints enable one to determine whether further specific therapy is needed and in non susceptible cases whether aspiration is sufficient or open drainage is necessary

Fluid aspiration, followed by injection of air or lipiodol, may be valuable when visualization of the joint space is desired The use of air, which is readily absorbed and causes little or no irritation, is preferable Subsequent X-ray examination indicates whether or not the joint space is in communication with surrounding bursae or pouches

There is little question about the safety of joint aspiration None of the 2 200 or more aspirations performed in this clinic has been followed by a joint infection With preparation of the region both 12 hours before and at the time of aspiration, and with ordinary aseptic precautions, the danger is negligible

The danger of serious bleeding exists only in hemophilia However, even in this disease, aspiration is safe if the clotting time has been brought to normal by transfusion in the previous 12 to 24 hours Withdrawal of bloody fluid from hemophilic joints is often indicated to relieve the severe pain and to prevent marked inflammatory changes in the synovial membrane

Mucin nitrogen and glucosamine were determined by precipitation with 1 per cent acetic acid and re precipitation with acetic acid from a 0 1 per cent sodium carbonate solution [170] Either the difference in total nitrogen or glucosamine before and after precipitation or the nitrogen or glucosamine of the precipitated mucin represents the mucin nitrogen or glucosamine Albumin and globulin contents were determined either by a modification of the Howe method[91] or by the method of Butler and Montgomery [23] The fibrinogen content of a few fluids was determined by the Cullen and Van Slyke method,[4] the nitrogen was measured by digestion and nesslerization However, as most of the fluids contained too little fibrinogen for determination by this method, the amount was estimated on the basis of the size of the clot formed Clots were classified as small (+), moderate (++) and large (+++) In the few fluids that contained sufficient fibrinogen for chemical analysis, solid clots formed within a few minutes after aspiration In general the large sized clots formed soon after withdrawal, whereas the formation of small clots frequently took many hours

The electrophoretic experiments were performed at 1 5° C in the apparatus described by Tiselius[200a] equipped with the Schlieren scanning device of Longsworth [120a] Before electrophoresis, the plasma was diluted with buffer to make a final concentration of 3 0 mg protein nitrogen per cc, or 1 87 per cent The solution was then dialyzed for three days with daily change of buffer The buffer used in all experiments was 0 1 N sodium di ethyl barbiturate and 0 02 N free barbituric acid pH 8 6, ionic strength 0 1

## INDICATIONS FOR ASPIRATION

The diagnostic and prognostic value of the information derived from the examination of synovial fluid is established in the present series making the chief indications for joint aspiration obvious There are also, however, certain therapeutic indications Whatever the purpose, the benefits of aspiration can be obtained without danger or marked discomfort to the patient

Withdrawal of fluid gives marked relief in massive effusions of traumatic or infectious origin which cause severe pain either by their size or rapidity of formation and resultant stretching of

examination, laboratory and X ray studies and a follow-up of the patient after discharge from the hospital Questionable cases have been excluded from the series

Analysis of all of the findings indicates that pathological synovial fluids in general can be divided into two large groups which will be designated in the following discussion as Group I and Group II Group I consists chiefly of cases in which an inflammatory reaction* of traumatic origin is present This includes fluids from all types of traumatic arthritis (including those with injury to the semilunar cartilages and those with hemorrhagic effusions), osteochondritis dissecans, degenerative joint disease, neuroarthropathy (Charcot joints), and osteochondromatosis Group II includes fluids from all types of infectious arthritis of known origin (streptococcal, staphylococcal, pneumococcal, gonococcal, meningococcal, *E coli*, bacteroides, tuberculous, syphilitic and those of Haverhill fever, bacillary dysentery, and German measles), from Reiter's syndrome and from rheumatoid arthritis Effusions in lupus erythematosus disseminatus, hypertrophic pulmonary osteoarthropathy and hemophilia resemble the fluids of Group I in most respects Fluids from rheumatic fever, gout, hemorrhagic villous synovitis and synovial tumors of various types resemble each group in certain respects

## INTRA-ARTICULAR PRESSURE

In human knee joints without effusions, the intra-articular pressure, as found by Muller,[135] is −8 to −12 cm of water

The intra articular pressure in joint disease in this series varied markedly and showed no correlation with the etiology, severity or duration Great variation was found also by Ranke[159] and Rostock[172] A significant relationship between intra-articular pressure and the concentration of sugar in the fluid was indicated, however, as will be discussed later The changes in sugar concentration with pressure, however, are not of diagnostic significance

## AMOUNT OF FLUID

The amount of fluid obtained (post mortem) from normal knee joints in our series ranged from 0 13 to 3 5 cc[171] Ragan[155] obtained similar amounts, ranging from 1 0 to 4 0 cc

*The term "inflammation" is used to indicate disorders of permeability circulation and metabolism resulting from any type of tissue injury

# II

## *Variations in Characteristics of Synovial Fluid with Disease*

THE following interpretations of the changes found in the cytological and chemical characteristics of synovial fluid in various diseases are based on studies of approximately 1,500 fluids Com parison of the data is valuable because fluids from all types of joint disease have been studied by similar techniques The studies reported by other investigators will be referred to throughout the discussion

The classification of joint diseases used is that approved by the Nomenclature Committee of the American Rheumatism Association[153] Rheumatoid arthritis (proliferative arthritis, atrophic arthritis, chronic infectious arthritis) includes Marie Strumpell spondylitis, Still s disease and a combination of psoriasis and generalized progressive arthritis The term 'intermittent hydrarthrosis refers to cases of unknown etiology in which joint effusions recur with amazing regularity at constant intervals A similar phenomenon occurs in some patients with definite rheumatoid arthritis, and it is probable that many patients with so called idiopathic intermittent hydrarthrosis are actually atypical cases of rheumatoid arthritis In the present series, there are only 2 cases of intermittent hydrarthrosis in which a diagnosis of rheuma toid arthritis cannot be made with certainty Even these 2 cases have clinical and laboratory findings suggestive of rheumatoid arthritis, as, for example, an elevated erythrocyte sedimentation rate in one and a progressive thickening of synovial tissues of both knees in the other The accuracy of the diagnosis in all cases has been controlled as fully as possible by history, physical

destruction of tissue On microscopic examination such fluids were found to contain numerous cholesterol crystals

BACTERIOLOGY AND IMMUNOLOGY

Normal synovial fluid is sterile Group I fluids are also sterile The findings in cultures from Group II fluids vary with the etiology of the disease

Cultures of fluid from 150 cases of rheumatoid arthritis in this series were negative, even though cultured aerobically and under 10 per cent $CO_2$ on boiled blood ascitic agar and broth and on blood agar plates and in anaerobic meat tubes Inoculations into chick embryos and intravenous, intra articular and intracerebral injections into mice also gave negative results

Positive synovial fluid cultures are essential in order to prove the diagnosis of infectious arthritis In this series, positive cultures were usually obtained in the cases in which joint infection by streptococcus, staphylococcus, pneumococcus or *E coli* was suspected

In fluid from tuberculous arthritis, the presence of organisms was proved by guinea pig inoculations in 21 of the 29 cases tested Positive cultures for tubercle bacilli were obtained in 3 of 5 cases

Fluids from patients with meningococcal arthritis yielded positive cultures only within the first few days after the onset of arthritis Although organisms were seen in the smears during the subsequent few days, they did not grow on culture Thereafter, no organisms were seen, and cultures, even from purulent fluids, were negative Whether or not this was due to an alteration of the organism produced by the antibiotics used to treat the generalized meningococcal infection is impossible to say Such a possibility is suggested by the recently demonstrated changes in the form of organisms produced by penicillin and streptomycin.[5] [133]

In many cases of probable gonococcal arthritis and in 14 cases of apparent specific infectious arthritis associated with purulent foci (such as empyema, pneumonia, mastoiditis, pelvic abscess and osteomyelitis) caused by *B hemolytic Streptococcus, Staphylococcus aureus* or *Pneumococcus*, type 7 or 23, cultures were negative Apparently the organisms reached the synovial tissues

The amount obtained in any one aspiration in the present series varied markedly, the minimum and maximum being 0 1 cc and 240 cc In all cases, with the exception of a few in which special studies were made, as much fluid as possible was withdrawn No definite correlation between the size of the effusion and the etiology, severity or duration of the joint disease was found In acute effusions, the amount of fluid decreased, of course, as the inflammation subsided Similarly, in the majority of rheumatoid patients receiving either adrenocorticotrophic hormone or cortisone,* the volume of effusions decreased

### GROSS APPEARANCE OF FLUID

Normal synovial fluid is clear, pale yellow and viscous and does not clot

The gross appearance of fluid is in itself of diagnostic significance In effusions from the types of joint disease included in Group I, it is similar to that of normal fluid relatively clear, pale yellow, fairly viscous and usually not clotting or forming only small, friable clots In cases of traumatic arthritis or synovial tumor in which hemorrhage has occurred in the past, the fluids are red or, if aspirated late, have a deeper yellow color due to pigments from destroyed hemoglobin In 88 traumatic fluids Kling[115] found an average icteric index of 14 with a range from 8 to 133 Occasionally globules of free fat are seen on the surface of fluids obtained from severe traumatic arthritis The fat is released, apparently, by injury to periarticular tissues or bone marrow

Fluids of Group II, in contrast, are usually turbid and much less viscous and the majority of them coagulate, often forming large firm clots The turbidity increases and viscosity decreases roughly in proportion to increasing severity of the joint disease Fluids from severe cases frequently show moderate amounts of debris, including small shreds of fibrin and amorphous material presumably resulting from cellular disintegration In 2 cases of severe rheumatoid arthritis of long duration the fluids were deep orange and contained free fat, large amounts of amorphous material and many flecks of fibrin, findings which indicate marked

*We are indebted to Armour Laboratories Armour and Company Chicago for the adrenocorticotrophic hormone and to Merck and Company Inc Rahway New Jersey for the cortisone used in these studies

present series, the Wassermann or gonococcal complement fixation test was positive in the joint fluid, even though it was negative in the serum and in fluid aspirated from another joint at the same time. Such "false positive" reactions in the absence of history, signs or symptoms compatible with syphilis or gonorrhea may be assumed to be non specific and of no diagnostic significance. Similar unverified "false positive" reactions are given occasionally by serum and other body fluids and have been found by others in synovial fluid[104, 116]

Further evidence that the synovial tissues are permeable to antibodies was found in a case of bacillary dysentery with joint involvement in which the agglutinin titer in the fluid to the Hiss Y strain of *Sh. dysenteriae* was 1/180 compared with 1/320 in the blood. Similarly, in a case of *Pneumococcus* (type 23) mastoiditis with associated arthritis, the agglutinin titers in blood and fluid were equal (positive in a dilution of 1/16). Increasing agglutinin titers in the fluid, corresponding to increases in the blood, were found also by Labor and von Balogh[119] in arthritis associated with bacillary dysentery. Agglutination titers for *B. tularense* of 1:1024 and 1:512 were found by Foshay and Mayer[75] in fluids from an olecranon bursitis in a patient with tularemia of 4 months duration. The titer in the serum corresponding to the latter fluid was 1:640.

Similarly, fluid and blood had the same bactericidal activity for hemolytic streptococci in 11 of 14 patients with various joint diseases studied by De Gara.[0] The activity against *E. coli* was alike in fluid and blood in 8 of 15 cases. In 40 fluids tested by De Gara, bactericidal activity for hemolytic streptococci was present in only 11 per cent (2 cases of rheumatoid arthritis, 1 of non specific infectious arthritis and 1 of intermittent hydrarthrosis), whereas bactericidal activity for *E. coli* was found in 87 per cent.

CYTOLOGY

*Leukocytes*

The total nucleated cell count of normal human fluid in our series varied from 13 to 180, with an average of 63 per cu. mm. The average differential count is: polymorphonuclears 6.5 per cent, lymphocytes 24.6 per cent, monocytes 47.9 per cent, clasmatocytes 10.1 per cent, unclassified phagocytes 4.9 per cent,

in these cases, causing inflammation and effusion, but were not present in the fluid in sufficiently large numbers to be cultured These findings are in accord with the results of post mortem examination of synovial tissue and synovial fluid from patients having generalized infection without joint symptoms[15] The synovial tissues in such cases showed moderate or marked inflammatory changes consisting of perivascular and often diffuse infiltration with polymorphonuclear and mononuclear leukocytes Occasionally, sharply defined acute inflammatory lesions were observed with marked infiltration of polymorphonuclears and mononuclears fibrin deposition, tissue necrosis and thrombosis of arterioles. The synovial fluids showed corresponding increases in the total leukocyte and polymorphonuclear counts, as was observed in similar cases by Labor and von Balogh[119]

Changes in the membrane comparable to those described above are presumably the basis for the joint pains that occur frequently in severe generalized infections Apparently organisms enter the synovial tissues in such infections, but the extent of the resulting joint involvement is determined by virulence and resistance and may be merely an arthralgia or a definite arthritis in which organisms cannot be cultured from the fluid, or a truly purulent arthritis

In normal synovial fluid Maunsell, Wrigley, Highton and Holt[127a] found no anti-A or anti B iso agglutinins or diphtheria immune antibodies However, four weeks after injection of diphtheria P T A P, in a normal control, the synovial fluid titer was 15 units per cc compared with a serum titer of more than 200 units per cc In patients with joint diseases (rheumatoid arthritis, osteoarthritis, infectious arthritis, intermittent hydrarthrosis and gout), the titers of anti A and B antibodies were approximately the same in fluid and serum Similarly after injection of P T A P in a patient with osteoarthritis, the titers in fluid from both knees (30 and 40 units per cc ) were almost as high as those of the sera (50 and 60 units)[127a]

Specific joint involvement is not necessarily indicated by the complement fixation test It is usually positive in the fluid when it is positive in the serum Spink and Keefer,[190] however in a series of 70 cases reported 47 positive tests in 54 blood samples compared with 21 positive in 35 joint fluids Occasionally in the

TABLE III Variations in Cytology of Synovial Fluid with Duration of Effusion

| Case number | Diagnosis | Joint | Duration of effusion | Amount cc | Total per cu mm | Leukocytes per cent‡ P | L | M |
|---|---|---|---|---|---|---|---|---|
| 1 | Traumatic arthritis with hemorrhage | Knee L | 4 weeks | 80 | 4 000 | 10 | 27 | 63 |
| | | L | 5 weeks | 12 | 600 | 0 | 67 | 33 |
| 2 | Traumatic arthritis with hemorrhage | L | 5 days | 20 | 750 | 19 | 48 | 33 |
| | | L | 31 days | 10 | 100 | 4 | 66 | 30 |
| 3 | Rheumatic fever | R | 1 day | 10 | 7 700 | 49 | 2 | 49 |
| | | R | 2 days | 0 2 | 2 900 | 27 | 12 | 61 |
| 4 | Rheumatic fever | L | 2 days | 12 | 12 300 | 87 | 2 | 11 |
| | | L | 5 days | 0 4 | 2 600 | 22 | 10 | 68 |
| | | R | 12 hours | 20 | 13 800 | 74 | 8 | 18 |
| | | R | 3½ days | 5 | 1 980 | 22 | 18 | 60 |
| 5 | Rheumatoid arthritis | R | 4 weeks | 12 | 51 600 | 95 | 2 | 3 |
| | | R | 5 weeks | 12 | 10 000 | 87 | 2 | 11 |
| | | R | 5 months | 35 | 19 600 | 74 | 18 | 8 |
| 6 | Rheumatoid arthritis | L | 3 days | 6 | 22,200 | 86 | 0 | 14 |
| | | L | 5 days | 12 | 13 750 | 85 | 3 | 12 |
| | | L | 2 months | 3 | 3 000 | 80 | 8 | 12 |
| 7 | *Probable rheumatoid arthritis* | R | 14 hours | 55 | 22 600 | 76 | 24 | 0 |
| | | R | 22 days | 20 | 9 000 | 61 | 33 | 6 |
| 8 | Intermittent hydrarthrosis | R | 2 days | 120 | 1 300 | 60 | 8 | 32 |
| | | R | 6 days | 6 | 5 250 | 0 | 50 | 42 |
| 9 | Gonococcal arthritis | L | 2 weeks | 20 | 22 000 | 82 | 8 | 10 |
| | | L | 3 weeks | 10 | 2 000 | 54 | 21 | 25 |
| 10 | Gonococcal arthritis | L | 3 days | 50 | 9 000 | 72 | 20 | 8 |
| | | L | 10 days | 60 | 1 300 | 68 | 20 | 12 |
| 11 | Gonococcal arthritis* | L | 1 week | 60 | 41 000 | 98 | 1 | 1 |
| | | L | 9 days | 25 | 13 200 | 98 | 2 | 0 |
| | | L | 2 weeks | 2 | 1 000 | 6 | 79 | 15 |
| 12 | Gonococcal arthritis* | L | 5 days | 150 | 22 300 | 54 | 46 | 0 |
| | | L | 1 week | 85 | 16 000 | 91 | 6 | 3 |
| | | L | 2 weeks | 60 | 29 100 | 86 | 14 | 0 |
| | | L | 5 weeks | | 12 200 | 2 | 98 | 0 |
| | | L | 6 weeks† | 10 | 18 900 | 68 | 32 | 0 |
| 13 | Gonococcal arthritis* | L | 8 days | 100 | 25 000 | 98 | 2 | 0 |
| | | L | 18 days | 40 | 17 900 | 58 | 42 | 0 |
| | | L | 32 days | 18 | 4 800 | 52 | 48 | 0 |
| 14 | Staphylococcal arthritis | L | 5 days | 5 | 151 500 | 89 | 2 | 9 |
| | | L | 8 days | 10 | 90 000 | 88 | 3 | 9 |
| | | L | 9 days | 10 | 81 500 | 97 | 1 | 2 |
| 15 | Infectious arthritis (negative culture) | L | 2 days | 35 | 20 000 | 98 | 0 | 2 |
| | | L | 4 days | 1 | 17 500 | 75 | 15 | 10 |
| 16 | Meningococcal arthritis | R | 2 days | 60 | 289 000 | 97 | 0 | 3 |
| | | R | 4 days | 18 | 14 600 | 98 | 0 | 2 |

‡P = polymorphonuclears L = lymphocytes M = mononuclear phagocytes
*Treated with sulfanilamide
†Exacerbation of joint symptoms
See also Figure 5 and Figure 8

(Table III continued on p 26)

synovial cells 4 3 per cent Similar nucleated cell counts were reported by Labor and von Balogh[119] (10 to 20 cells per cu mm), McEwen[1-8] (125 to 200 cells per cu mm) and Kling[11] (10 to 50 cells per cu mm) Davies[45] found a range of cell counts from 80 to 481 in 7 normal human fluids It is of interest that his studies in fluids from animals[46] revealed lower cell counts in the joints of the extremities than in those of the head and neck

Variations in cytology in joint effusions are related not only to the type of joint disease but also to its severity and duration By means of the total leukocyte and absolute polymorphonuclear cell counts, Group II fluids can be differentiated from those of Group I in almost all cases (Figures 5 and 6 and the chart at the back of the book) As shown by Figure 5, the total count was below 3,000 in 133 of 142 Group I fluids and above 3,000 in 363 of 405 Group II fluids Similarly, the absolute polymorphonuclear count was below 500 in Group I fluids and above 500 in Group II fluids (Figure 6)

Differentiation within either Group I or Group II cannot usually be made on the basis of cytological findings alone because of their variation with the severity of the disease and the duration of the effusion The cell counts of individual fluids in either group do, however, occasionally aid in differential diagnosis For example, neuroarthropathy, rather than traumatic arthritis, is suggested by a fluid with a low total leukocyte count but 40 to 50 per cent of polymorphonuclears Likewise, a total leukocyte count under 3,000 with few or no polymorphonuclears is more compatible with disseminated lupus than with rheumatoid arthritis and accords with the findings in blood and other body fluids in lupus Similarly total leukocyte counts above 100,000 have been found only in infectious arthritides *

The correlation of cytological findings with the severity of the inflammation in the involved joints was well demonstrated in the 5 cases of gonococcal arthritis in which aspirations of joints were performed at intervals during improvement (Table III) In Case 11, for example, the counts fell steadily from 41,000 per cu mm with 98 per cent polymorphonuclears to 1,000 with 6 per cent polymorphonuclears after 2 weeks The changes in

*Since this study was completed 1 fluid with a leukocyte count of 116 200 has been obtained from a patient with rheumatoid arthritis

TABLE IV Comparison of 9 Fluids with Positive Cultures and 33 Fluids with Negative Cultures in Gonococcal Arthritis

| | Negative culture | | | Positive culture | | |
|---|---|---|---|---|---|---|
| | Minimum | Maximum | Average | Minimum | Maximum | Average |
| Total leukocyte count, cells per cu. mm | 1 535 | 108 000* | 14 070 | 31 500 | 290 000 | 106 530 |
| Polymorphonuclears per cent | 2 | 98 | 65 | 90 | 99 | 95 |
| Sugar mg per 100 cc | 49 | 113 | 83 | 0 | 63 | 29 |
| Relative viscosity at 25 C | 3 | 19 | 12 | | | 4† |
| Total protein gm per 100 cc | 4 3 | 6 9 | 5 3 | 5 3 | 6 0 | 5 6 |
| Globulin, gm per 100 cc | 1 3 | 3 1 | 2 0 | 2.2 | 2 7 | 2 5 |
| Mucin nitrogen gm per 100 cc | 016 | 158 | 064 | 0 | 077 | 041 |

*Patient had been receiving sulfanilamide before the fluid was cultured
†Value determined in only 1 fluid.

In rheumatoid arthritis it is frequently impossible to evaluate the degree of joint inflammation in any one joint, and as a result correlation of the cytological findings with the severity of the disease process in the joints is difficult There is little evidence of any variation with severity when cell counts are compared with estimates of the severity of the disease as a whole in individual patients (see Table VII) A possible relationship between cytology and the estimated severity of the process in individual joints has, however, been indicated in some cases These patients have been followed for several years after the initial aspiration, and the course of the disease in the aspirated joint has been used as indication of the severity in that joint at the time it was tapped It appears from the cases thus studied that the height of the total leukocyte and absolute polymorphonuclear counts early in the disease may correspond to the severity of the joint involvement and indicate, to some extent, the prognosis For example, two of the highest fluid counts in the series (66,000 and 40,000 cells per cu mm ) were from knees which have since become progressively worse, with increasing thickening of periarticular tissues and narrowing of the joint spaces Fluid aspirated 5 years after the initial joint tap was very turbid and contained free fat and cholesterol crystals, both indicative of marked tissue destruction

TABLE III Variations in Cytology of Synovial Fluid with Duration of Effusion (*continued*)

| Case number | Diagnosis | Joint | Duration of effusion | Amount, cc | Total per cu mm | Leukocytes per cent P | L | M |
|---|---|---|---|---|---|---|---|---|
| 16 | Meningococcal arthritis (*continued*) | Knee | | | | | | |
| | | R | 13 days | 20 | 54 400 | 95 | 0 | 5 |
| | | R | 20 days | 15 | 46 000 | 95 | 3 | 2 |
| | | R | 25 days | 2 | 21 850 | 87 | 8 | 5 |
| | | L | 6 days | 20 | 36 600 | 96 | 2 | 2 |
| | | L | 8 days | 7 | 61 200 | 99 | 0 | 1 |
| | | L | 10 days | 4 | 49 800 | 95 | 3 | 2 |
| 17 | Meningococcal arthritis | R | 10 hours | 10 | 159 500 | 98 | 1 | 1 |
| | | R | 30 hours | 65 | 76 500 | 93 | 0 | 7 |
| | | R | 2 days | 45 | 38 950 | 95 | 1 | 1 |
| | | R | 8 days | 60 | 25 750 | 99 | 1 | 0 |
| | | R | 15 days | 32 | 24 000 | 96 | 1 | 3 |
| | | R | 19 days | 12 | 8 800 | 77 | 9 | 14 |
| | | R | 21 days | 4 | 5 950 | 68 | 19 | 13 |
| 18 | Meningococcal arthritis | Elbow | | | | | | |
| | | L | 1 day | 23 | 91 000 | 98 | | |
| | | L | 6 days | 8 | 124 500 | 97 | 0 | 3 |
| | | L | 8 days | 20 | 50 800 | 98 | 0 | 2 |
| | | L | 15 days | 2 | 53 500 | 95 | 3 | 2 |
| | | L | 16 days | 6 | 36 050 | 84 | 9 | 7 |
| | | R | 1 day | 10 | 81 000 | 98 | | |
| | | R | 6 days | 25 | 124 000 | 99 | 0 | 1 |
| | | R | 12 days | 8 | 35 400 | 84 | 2 | 14 |
| | | R | 17 days | 4 | 23 600 | 82 | 4 | 14 |
| | | Knee | | | | | | |
| | | L | 1 day | 28 | 87 000 | 98 | | |
| | | L | 4 days | 50 | 47 500 | 96 | 0 | 4 |
| 19 | Reiter's syndrome | Knee | | | | | | |
| | | L | 4 days | 70 | 44 300 | 89 | 1 | 10 |
| | | L | 16 days | 12 | 11 250 | 92 | 0 | 8 |
| | | L | 9 weeks | 11 | 14 950 | 90 | 0 | 10 |
| | | L | 12 weeks | 4 | 2,250 | 22 | 2 | 71 |
| 20 | Reiter's syndrome | L | 3 days | 70 | 20 700 | 84 | 9 | 7 |
| | | L | 4 weeks | 80 | 25 000 | 75 | 16 | 9 |
| | | L | 9 weeks | 10 | 9 200 | 56 | 10 | 34 |

cytology indicated a steady decrease in the inflammation of the synovial tissues and paralleled the clinical improvement as manifested by gradual subsidence of redness, tenderness pain and swelling (Some of the patients received only symptomatic treatment, while others were given sulfanilamide ) The influence of the severity of the joint involvement on cytological findings is apparent also in the marked difference between the counts in sterile fluids from gonococcal arthritis averaging 14 070 per cu mm and those in the fluids with positive cultures averaging 106,530 per cu mm (see Table IV)

GROUP II

| | | |
|---|---|---|
| Rheumatoid Arthritis | 146 | 191 |
| Probable Rheumatoid Arthritis | 45 | 45 |
| Reiter s Syndrome | 16 | 25 |
| Syphilitic Arthritis — Congenital | 13 | 16 |
| Tuberculous Arthritis | 25 | 28 |
| Gonorrheal Arthritis (290M) | 36 | 42 |
| Septic Arthritis (266M) | 37 | 40 |
| Meningococcal Arthritis (750M, 289M) | 11 | 18 |

⊗ fluids from traumatic arthritis of more than 3 months duration

⊖ fluids from degenerative joint disease secondary to other joint abnormality

○ fluids from rheumatoid arthritis of mild severity

◐ fluids from rheumatoid arthritis of moderate severity

⦶ fluids with positive cultures

● fluids of the types designated by the headings with the exception that the symbol indicates in traumatic arthritis fluids of less than 3 months duration in degenerative joint disease, primary degenerative joint disease in rheumatoid arthritis severe disease and in the infectious arthritides fluids with negative cultures

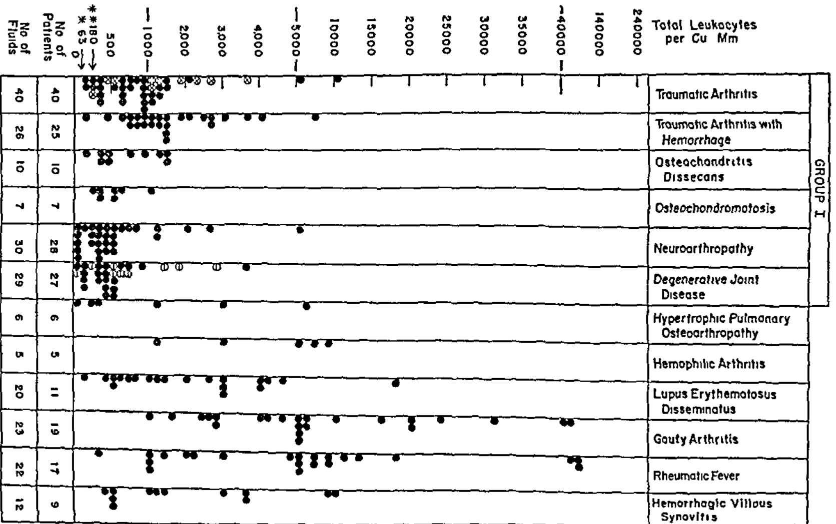



Figure 5 Total number of leukocytes per cu mm in synovial fluid from various joint diseases The asterisks represent the minimum and maximum values in normal fluids

GROUP II

| | | |
|---|---|---|
| Rheumatoid Arthritis | 136 | 181 |
| Probable Rheumatoid Arthritis | 45 | 45 |
| Reiter's Syndrome | 16 | 25 |
| Syphilitic Arthritis — Congenital | 12 | 15 |
| Tuberculous Arthritis | 24 | 27 |
| Gonorrheal Arthritis (287 M) | 35 | 40 |
| Septic Arthritis | 36 | 41 |
| Meningococcal Arthritis (727 M, 280 M) | 11 | 18 |

⊗ fluids from traumatic arthritis of more than 3 months duration

⊖ fluids from degenerative joint disease secondary to other joint abnormality

○ fluids from rheumatoid arthritis of mild severity

◐ fluids from rheumatoid arthritis of moderate severity

⦶ fluids with positive cultures

● fluids of the types designated by the headings with the exception that the symbol indicates in traumatic arthritis, fluids of less than 3 months duration, in degenerative joint disease, primary degenerative joint disease in rheumatoid arthritis, severe disease, and in the infectious arthritides fluids with negative cultures

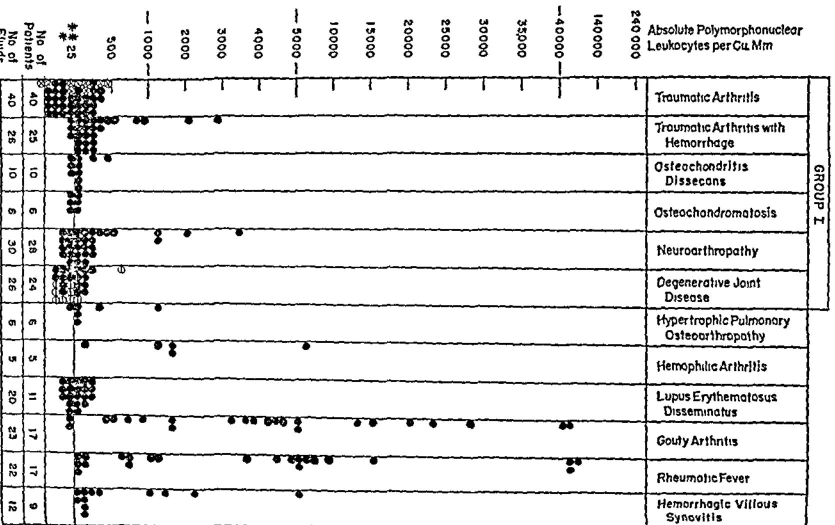



Figure 6 Absolute number of polymorphonuclears per cu mm in synovial fluid from various joint diseases The asterisks represent the minimum and maximum values in normal fluids

to Duration of Effusion (Rheumatoid Arthritis)

| Globulin gm per 100 cc Fluid | Globulin gm per 100 cc Serum | Relative viscosity at 38 C | Mucin nitrogen gm per 100 cc | Mucin glucosamine gm per 100 cc | Type of mucin precipitate |
|---|---|---|---|---|---|
| 1 2 ( 8) | 2 3 ( 8) | 4 3 ( 7) | 010 (16) | 033 ( 5) | VP ( 9) |
| 1 8 | 3 1 | 9 9 | 049 | 042 | P |
| 2 3 | 3 4 | 27 6 | 097 | 054 | G |
| 1 3 ( 4) | 2 6 ( 4) | 18 6 ( 2) | 020 (17) | 038 ( 3) | VP ( 5) |
| 1 9 | 3 1 | 19 0 | 079 | 058 | P |
| 3 3 | 3 8 | 19 3 | 131 | 076 | F |
| 1.2 (15) | 2 3 (11) | 2 8 (19) | 005 (26) | 006 ( 5) | VP (15) |
| 1 9 | 3 0 | 7 1 | 051 | 026 | P |
| 3 0 | 3 8 | 13 3 | 134 | 035 | F |
| 1 8 ( 3) | 2 8 ( 3) | 6 3 ( 2) | 028 (14) | 019 ( 6) | VP ( 4) |
| 1 9 | 3 3 | 26 2 | 068 | 041 | P |
| 2 0 | 3.5 | 46 | 130 | 067 | G |
| 1 3 (18) | 3 0 (13) | 3 7 (21) | 032 (32) | 006 (14) | VP (20) |
| 2 7 | 3 7 | 14 5 | 068 | 043 | F |
| 6 8 | 6 8 | 43 | 137 | 081 | G |

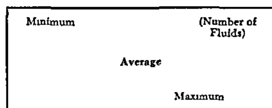
The type of precipitate is expressed in symbols having the following significance VP=few or no flecks in a cloudy solution P=small friable masses in a cloudy solution F=soft mass in a clear or slightly cloudy solution G=tight ropy clump in a clear solution. (See Figure 13 )

Comparison of the cytological findings in individual rheumatoid effusions of varying duration gives no evidence of a relationship between the total leukocyte and polymorphonuclear counts and the duration of the effusion (Table V) nor do the series of leukocyte counts on fluids from a patient whose knees were aspirated 24 times in the course of 16 months (Table VI) *Probably the cytological findings in these and in other chronic effusions are more influenced by temporary variations in the severity of the synovial tissue inflammation than by the duration of the effusion* There is, however a relationship between cytological findings and duration of effusion in the series of fluids obtained daily from a patient with generalized rheumatoid arthritis who had bilateral intermittent knee effusions recurring at constant intervals The effusions resembled those of idiopathic intermittent hydrarthrosis and appeared and disappeared in regular cycles with 6 days between the peaks (see Figure 7) In these effusions the total leukocyte count and percentage of polymorphonuclears rose during the period of increasing inflammation and then decreased rapidly during *subsidence* As the polymorphonuclears disappeared,

TABLE V Relation of Cytological and Chemical Findings in Synovial Fluid and Serum

| Duration of effusion | Clot | Total leukocytes per cu mm | Polymorpho nuclears per cent | Sugar mg per 100 cc Fluid | Sugar mg per 100 cc Serum | Protein (exclusive of mucin) gm per 100 cc Fluid | Protein (exclusive of mucin) gm per 100 cc Serum |
|---|---|---|---|---|---|---|---|
| Up to 1 week | 0 (18) | 1 100 (20) | 2 (19) | 24 (12) | 60 (12) | 3 6 (16) | 6 5 (14) |
| | 1 5 | 9,210 | 58 | 76 | 93 | 4 9 | 7 4 |
| | 4 | 42 700 | 92 | 132 | 125 | 5 8 | 8 2 |
| 1 week to 6 weeks | 0 (17) | 450 (22) | 0 (22) | 61 (17) | 84 (12) | 3 0 (19) | 6 1 (13) |
| | 1 3 | 13 130 | 68 | 80 | 96 | 4 6 | 7 4 |
| | 3 | 51 600 | 95 | 102 | 125 | 6 1 | 8 7 |
| 6 weeks to 6 months | 0 (36) | 2 020 (38) | 5 (38) | 27 (28) | 78 (23) | 3 3 (27) | 7 0 (19) |
| | 1 2 | 15 060 | 62 | 66 | 96 | 4 7 | 7 5 |
| | 3 | 62 200 | 91 | 116 | 129 | 6 2 | 8 7 |
| 6 months to 1 year | 0 (11) | 2 500 (18) | 8 (16) | 0 (14) | 75 (11) | 4 1 (14) | 6 6 ( 9) |
| | 1 4 | 12,400 | 73 | 63 | 93 | 4 7 | 7 3 |
| | 3 | 38 850 | 96 | 100 | 108 | 6 1 | 8 3 |
| 1 year + | 0 (34) | 610 (54) | 3 (51) | 0 (32) | 68 (26) | 3 6 (34) | 6 8 (22) |
| | 0 5 | 16,775 | 66 | 58 | 91 | 5 2 | 7 9 |
| | 3 | 66 000 | 94 | 102 | 116 | 8 9 | 10 1 |

The significance of the figures in each division is indicated in the following diagram




In contrast, one of the lowest counts in the series was in knee fluid from a patient who has since developed spondylitis but has had no evidence of inflammation in his knee for the past 10 years However, there are many exceptions to this apparent relationship and further study is necessary to determine how closely the cytological findings correspond to the severity in rheumatoid arthritis

The response of the fluid cytology to administration of adreno corticotrophic hormone or of cortisone gives further suggestion of a relationship with severity of tissue inflammation Either the total leukocyte count or the percentage of polymorphonuclears fell in almost all cases, the greatest decreases being from 30,800 cells per cu mm with 16 per cent polymorphonuclears to 150 cells with no polymorphonuclears and from 15,750 to 100 cells with 76 and 4 per cent polymorphonuclears respectively

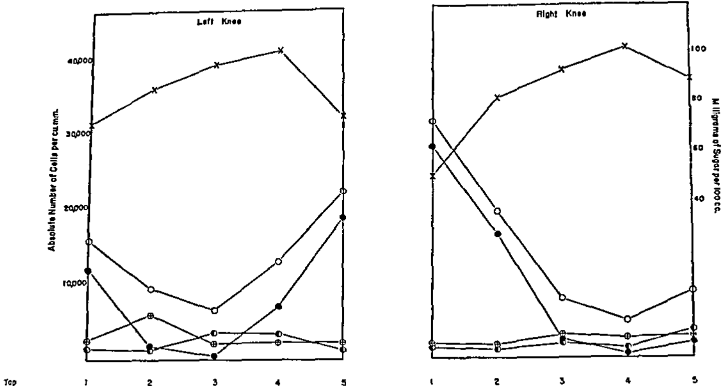



FIGURE 7 Cytological findings and concentration of glucose in series of fluids obtained daily from a patient with generalized rheumatoid arthritis who had bilateral intermittent knee effusions recurring at regular intervals Peaks of effusion occurred six days apart on day 3 of the cycle A series of five daily taps was made on each knee, omitting the left knee on day 3, and the right knee on day 2 of the cycle of effusion (See Table IX)

TABLE VI Total Leukocyte and Polymorphonuclear Counts in 24 Fluids Aspirated from Knees of a Patient with Rheumatoid Arthritis Over the Course of 16 Months

| | Leukocytes per cu mm | | Polymorphonuclears per cent | |
|---|---|---|---|---|
| Date | Left | Right | Left | Right |
| 12/30/37 | 12 100 | 9 100 | 80 | 89 |
| 1/11/38 | 25 000 | | 94 | |
| 1/20/38 | | 8 000 | | 77 |
| 1/21/38 | 8,200 | | 67 | |
| 1/25/38 | | 12 100 | | 84 |
| 2/ 5/38 | | 18 400 | | |
| 2/11/38 | 16 100 | | | |
| 2/14/38 | 14 800 | | 72 | |
| 2/18/38 | 17 800 | | 78 | |
| 2/26/38 | 15 800 | | 88 | |
| 3/ 1/38 | 13 400 | | 72 | |
| 3/ 9/38 | 27 200 | | 86 | |
| 3/10/38 | 13 500 | | 76 | |
| 3/24/38 | 19 000 | | 90 | |
| 4/ 1/38 | | | 80 | |
| 4/12/38 | 9 600 | | | |
| 4/22/38 | 9 300 | | 75 | |
| 4/24/38 | | 21 000 | | 86 |
| 11/30/38 | 10 100 | | 45 | |
| 12/ 3/38 | | 15 500 | | 51 |
| 12/ 7/38 | 11 500 | | 63 | |
| 4/ 7/39 | | 16 500 | | 90 |
| 4/ 8/39 | 25 800 | | 88 | |
| 4/10/39 | 11 400 | | | |

monocytes and clasmatocytes increased, while the absolute number of lymphocytes remained approximately constant The cytological variations that are related to the duration of the effusion are due essentially to changes in the degree of inflammation in the synovial membrane and give, therefore, further indication of the correlation with severity

A similar rise in percentage and absolute number of polymorphonuclears during increasing synovial inflammation and a subsequent replacement by monocytes and clasmatocytes and eventual replacement in part by lymphocytes was found in other types of joint disease (see Table III) This sequence of changes occurred most rapidly and was most marked in rheumatic fever It has been observed in this laboratory in 2 cases of traumatic arthritis with hemorrhage, in 2 cases of rheumatic fever in 3 cases of rheumatoid arthritis in 1 case of probable rheuma-

Figure 8 Cytological findings and concentration of glucose in a series of fluids obtained daily from a patient with intermittent hydrarthrosis

toid arthritis, in 2 cases of Reiter's syndrome, in 5 cases of gonococcal arthritis, and in 1 case of specific infectious arthritis with negative culture In meningococcal arthritis, the cytological changes during decreasing inflammation are similar in type but less marked and take place much more slowly than in gonococcal arthritis Similar cytological response was noted in 1 effusion in a case of idiopathic intermittent hydrarthrosis (Table III) In 2 other effusions in intermittent hydrarthrosis (1 in the above patient), there was no definite initial polymorphonuclear response, but the usual rise in monocytes occurred as the effusion increased (Figure 8) Krummel,[117] in 1 case of intermittent hydrarthrosis, found an increase in polymorphonuclears and monocytes with increasing effusion and a rise in lymphocytes with subsiding effusion It is apparent that the polymorphonuclear rise is not always detectable in intermittent hydrarthrosis, but there is always a response of mononuclear phagocytes

The initial rapid rise in polymorphonuclears and subsequent replacement by mononuclear phagocytes and eventually by lymphocytes found in so many types of joint disease is the same as the cytological reaction produced by the injection of normal saline into a rabbit's knee joint [205] Apparently such mild irritation produces sufficient change in the subsynovial capillaries to allow for an immediate intra articular migration of polymorphonuclear leukocytes, whereas the mononuclear phagocytes arising from the synovial tissue and tissue fluids are much slower to respond [108a] Further evidence that this cytological picture represents the usual reaction of synovial tissue to irritation is obtained from reports by other investigators[39 66 103 112 119 163] of a predominance of polymorphonuclears in acute effusions of various types and a preponderance of lymphocytes in chronic joint conditions with less acute inflammation The magnitude of the cellular response varies with the degree of tissue irritation but the pattern apparently is similar in all cases and represents the fundamental cytological reaction to inflammation which was first described by Borrel,[23] Durham[58] and Beattie[14] Menkin and Warner[130] concluded from the results of studies of inflammatory reactions produced in the pleural cavities of dogs, that this cytological sequence is conditioned by the local pH of the inflamed area,

PROTEIN

In normal human fluid, the total protein content (exclusive of mucin) varied in our series from 1 07 to 2 13 gm per 100 cc Most of this protein is albumin The albumin/globulin ratio in the only normal fluid analyzed was 20 4[171] Similar values for total protein were found by Fisher[67] (1 6 per cent) and Honye[90] (0 45 to 3 15 per cent)

The concentration of total protein in joint effusions varies markedly and shows significant relationships with the type of joint disease and the duration and severity of the process Group I fluids, in general, have concentrations two to three times higher than normal but lower than those of Group II fluids, the maximum in Group I being 5 5 gm per 100 cc (Figure 9 and the chart at the back of the book) Fluids from cases of osteochondromatosis and lupus erythematosus disseminatus have lower protein contents than any other pathological fluids, containing only slightly more than normal fluids (averaging 2 2 and 2 5 gm per 100 cc ) Slightly higher values are found in fluids from degenerative joint disease, hypertrophic pulmonary osteoarthropathy, osteochondritis dissecans, Charcot joints, rheumatic fever, traumatic arthritis (including derangement of the semilunar cartilage) tumors and gout Traumatic effusions that are hemorrhagic and those of over 3 months duration show a slightly higher average protein content than other traumatic fluids The effusions of hemophiliac arthritis, which resemble Group I fluids in most respects contain much more protein Fluids of Group II have a higher average concentration of total protein (4 9 gm per 100 cc ) Variations are more marked in rheumatoid fluids than in any other group with a minimum of 2 7 gm per 100 cc, a concentration typical of fluids of Group I and a maximum of 8 89 the highest protein concentration found in any fluid of any kind Analysis of these variations in rheumatoid cases shows that there is a tendency toward correlation with the severity of the disease and its duration and with duration of the effusion In this series the differences between the average protein contents of effusions from severe (5 2 gm per 100 cc ) moderate (5 0 gm ) and mild cases (4 6 gm ) were statistically significant at the 5 per cent level (Table VII) Similarly, the fluid protein concentration increased slightly with duration of the disease (Table VIII) and

polymorphonuclear cells predominating when the exudate is more alkaline than pH 7 0

Eosinophils, which are not found in normal fluid, were found in only 13 fluids in the present series, and in all but 2 cases were present in a concentration of only 1 per cent In all but 3 of these cases the fluids contained blood, 3 of the patients having hemophilia, 4, traumatic arthritis with hemorrhage, 1, hemorrhagic villous synovitis, 1, rheumatic fever, 1, neuroarthropathy, 1, traumatic arthritis, and 2, rheumatoid arthritis

*Erythrocytes*

Erythrocytes are not normal constituents of synovial fluid [171] They may be noted in varying numbers in pathological effusions but are usually not of diagnostic significance However, aspiration of hemorrhagic fluid in the absence of a history of recent severe trauma or hemophilia would suggest the presence of a tumor of the type classified as xanthomatous giant cell tumor or hemorrhagic villous synovitis or possibly a Charcot joint

In summary, it can be concluded that an effusion in which the leukocyte count is above 5,000 per cu mm or the absolute polymorphonuclear count above 500 per cu mm is probably not traumatic in origin The total leukocyte and the polymorphonuclear counts rise with increasing severity of synovial tissue inflammation and can be used as indications of the course of the synovitis in acute effusions especially in infectious arthritis

SPECIFIC GRAVITY AND TOTAL SOLIDS

The content of total solids in normal human fluid in our series ranged from 2 40 to 4 83 gm per 100 gm, with an average of 3 41 gm The normal specific gravity has not been determined In fluids obtained from patients with edema, it ranged from 1 008 to 1 012 Horiye[90] reported total solids of 1 20 to 3 90 per cent and specific gravities ranging from 1 008 to 1 015 for normal human fluids obtained post mortem The figure given by Fisher[67] for total solids is slightly higher (4 4 per cent)

The specific gravity and content of total solids in fluids of Group I are much higher than those of normal fluid but tend to be slightly lower than those of Group II fluids This is in accord with the difference in protein content which will be discussed later

| GROUP II | | |
|---|---|---|
| Rheumatoid Arthritis | 96 | 131 |
| Probable Rheumatoid Arthritis | 17 | 17 |
| Reiter's Syndrome | 10 | 12 |
| Syphilitic Arthritis — Congenital | 9 | 11 |
| Tuberculous Arthritis | 8 | 9 |
| Gonorrheal Arthritis | 25 | 27 |
| Septic Arthritis | 13 | 16 |
| Meningococcal Arthritis | 2 | 2 |

89

‡

- ⊙ fluids from traumatic arthritis of more than 3 months duration
- ⊖ fluids from degenerative joint disease secondary to other joint abnormality
- ○ fluids from rheumatoid arthritis of mild severity
- ◐ fluids from rheumatoid arthritis of moderate severity
- ⦶ fluids with positive cultures
- ● fluids of the types designated by the headings with the exception that the symbol indicates in traumatic arthritis fluids of less than 3 months duration in degenerative joint disease, primary degenerative joint disease in rheumatoid arthritis severe disease and in the infectious arthritides, fluids with negative cultures
- ‡ a fluid from a patient with severe renal disease due to amyloidosis

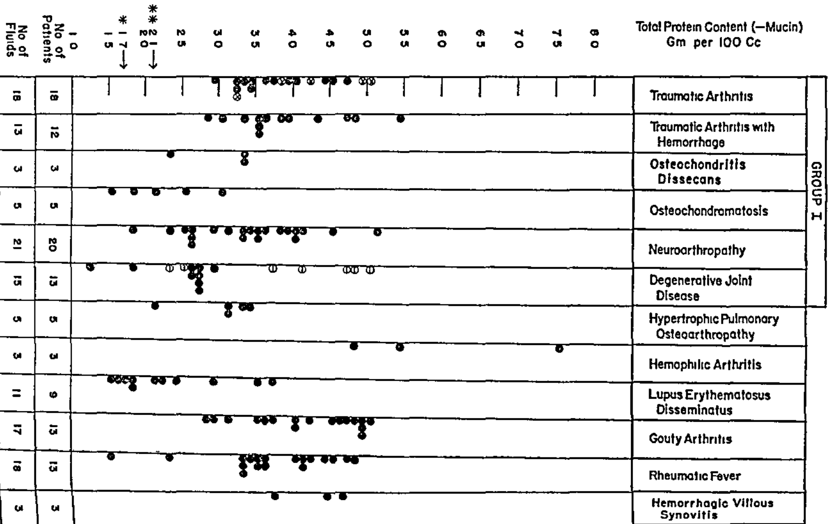



FIGURE 9 Concentration of total protein (exclusive of mucin) in synovial fluid from various joint diseases The asterisks represent the minimum and maximum values in normal fluids

to Severity of Disease (Rheumatoid Arthritis)

| Globulin gm per 100 cc Fluid | Globulin gm per 100 cc Serum | Relative viscosity at 38 C | Mucin nitrogen gm per 100 cc | Mucin glucosamine gm per 100 cc | Type of mucin precipitate |
|---|---|---|---|---|---|
| 1 0 (17) | 2 0 (34) | 3 9 (19) | 007 (41) | 026 ( 9) | VP (20) |
| 1 8 | 2 7 | 12 1 | 073 | 046 | P |
| 2 3 | 3 4 | 28 | 166 | 072 | G |
| 1 2 (34) | 2 0 (88) | 3 4 (23) | 005 (67) | 022 (13) | VP (26) |
| 2 3 | 3 1 | 13 5 | 060 | 037 | F |
| 4 7 | 5 1 | 46 | 137 | 081 | G |
| 0 8 ( 7) | 2 4 (41) | 3 5 ( 8) | 010 (17) | 006 ( 7) | VP ( 7) |
| 2 8 | 3 7 | 7 1 | 061 | 038 | VP |
| 6 8 | 7 1 | 9 7 | 131 | 025 | F |

The type of precipitate is expressed in symbols having the following significance VP=few or no flecks in a cloudy solution P=small friable masses in a cloudy solution F=soft mass in a clear or slightly cloudy solution G=tight ropy clump in a clear solution (See Figure 13 )

*Serum to Duration of Disease (Rheumatoid Arthritis)*

| Globulin gm per 100 cc Fluid | Globulin gm per 100 cc Serum | Relative viscosity at 38 C | Mucin nitrogen gm per 100 cc | Mucin glucosamine gm per 100 cc | Type of mucin precipitate |
|---|---|---|---|---|---|
| 1.2 ( 4) | 2 3 ( 7) | ( 1) | 050 (10) | | P ( 2) |
| 1 4 | 2 8 | 5 5 | 087 | | F |
| 1 5 | 3 5 | | 131 | | F |
| 1 0 (13) | 2 0 (26) | 3 5 (14) | 007 (28) | 006 ( 5) | VP (17) |
| 1 9 | 2 8 | 9 0 | 051 | 025 | P |
| 2 5 | 4 6 | 28 | 134 | 036 | G |
| 1 3 (19) | 2 4 (38) | 2 8 (19) | 005 (51) | 022 ( 9) | VP (17) |
| 2 6 | 3 4 | 13 6 | 063 | 048 | F |
| 4 5 | 5 6 | 46 | 130 | 081 | G |
| 0 8 (18) | 2 0 (57) | 3 4 (16) | 006 (28) | 006 (12) | VP (15) |
| 2 3 | 3 2 | 12 9 | 071 | 040 | F |
| 6 8 | 6 8 | 43 | 137 | 076 | G |

The type of precipitate is expressed in symbols having the following significance VP=few or no flecks in a cloudy solution P=small friable masses in a cloudy solution F=soft mass in a clear or slightly cloudy solution G=tight, ropy clump in a clear solution (See Figure 13 )

TABLE VII Relation of Cytological and Chemical Findings in Synovial Fluid and Serum

| Severity | Total leukocytes per cu mm | Polymorphonuclears per cent | Sugar mg per 100 cc Fluid | Sugar mg per 100 cc Serum | Protein (exclusive of mucin) gm per 100 cc Fluid | Protein (exclusive of mucin) gm per 100 cc Serum |
|---|---|---|---|---|---|---|
| | 450 (62) | 0 (59) | 24 (35) | 60 (32) | 3 5 (42) | 6 5 (58) |
| Mild | 13,420 | 55 | 80 | 98 | 4 6 | 7 4 |
| | 52 800 | 96 | 126 | 129 | 6 0 | 8 3 |
| | 610 (101) | 3 (95) | 0 (67) | 56 (46) | 3 3 (71) | 4 8 (127) |
| Moderate | 15 620 | 68 | 60 | 93 | 5 0 | 7 5 |
| | 68 000 | 96 | 132 | 121 | 7 0 | 9 2 |
| | 1 750 (28) | 44 (26) | 0 (19) | 75 (14) | 2 7 (17) | 5 9 (53) |
| Severe | 18,380 | 76 | 56 | 93 | 5.2 | 7 6 |
| | 62 200 | 92 | 101 | 106 | 8 9 | 10 4 |

The significance of the figures in each division is indicated in the following diagram

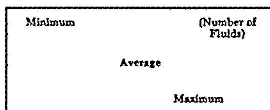



TABLE VIII Relation of Cytological and Chemical Findings in Synovial Fluid and

| Duration of disease | Clot | Total leukocytes per cu mm | Polymorphonuclears per cent | Sugar mg per 100 cc Fluid | Sugar mg per 100 cc Serum | Protein (exclusive of mucin) gm per 100 cc Fluid | Protein (exclusive of mucin) gm per 100 cc Serum |
|---|---|---|---|---|---|---|---|
| Up to | 1 (9) | 3,200 (14) | 36 (14) | 24 (8) | 80 (6) | 3 0 (11) | 6 1 (11) |
| 6 weeks | 2 | 17,114 | 75 | 73 | 91 | 4 5 | 7 2 |
| | 3 | 45 000 | 95 | 101 | 100 | 5 1 | 8 0 |
| 6 weeks | 0 (32) | 1 100 (41) | 8 (38) | 9 (28) | 60 (23) | 3 5 (30) | 6 2 (36) |
| to | 1 | 17,252 | 65 | 70 | 95 | 4 9 | 7 5 |
| 1 year | 3 | 62 200 | 96 | 116 | 129 | 5 8 | 8 6 |
| 1 year | 0 (60) | 450 (71) | 0 (68) | 0 (40) | 68 (28) | 3 6 (53) | 5 9 (60) |
| to | 0 8 | 17,005 | 65 | 59 | 94 | 4 9 | 7 8 |
| 5 years | 3 | 66 000 | 96 | 102 | 121 | 6 6 | 9 2 |
| | 0 (39) | 610 (49) | 3 (48) | 0 (38) | 75 (28) | 2 7 (30) | 4 8 (67) |
| 5 years + | 1 1 | 12 798 | 63 | 71 | 94 | 5 0 | 7 6 |
| | 3 | 43 800 | 95 | 132 | 125 | 8 9 | 10 1 |

The significance of the figures in each division is indicated in the following diagram

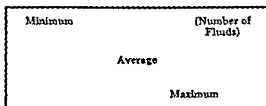


TABLE IX Variations in Concentrations of Albumin Globulin and Mucin in Intermittent Bilateral Knee Effusions in a Patient with Rheumatoid Arthritis*

| Day of effusion | | Amount † cc | | Total protein (exclusive of mucin) gm /100 cc | | | Globulin gm /100 cc | | | Mucin nitrogen gm /100 cc | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Rt. | Lt | Rt | Lt. | Se | Rt. Fl | Lt Fl | Se | Rt. Fl. | Lt. Fl. | Rt Fl. | Lt. Fl. |
| 3 | 4 | 20 | 20 | 9 1 | 6 5 | 5 9 | 4 6 | 3 7 | 3 6 | 062 | 066 |
| 4 | 5 | 18 | 13 | 8 7 | 6 0 | 6 3 | 4 5 | 3 5 | 4 2 | 087 | 025 |
| 5 | 0 | 20 | 1 | 8 7 | 6 1 | | 4 5 | 4 1 | | 060 | |
| 0 | 1 | 13 | 25 | 8 5 | 6 4 | 6 6 | 4 1 | | 4 0 | 016 | 039 |
| 1 | 2 | 12 | 60 | 8 5 | 6 6 | 6 5 | 4 0 | | 3 6 | 038 | 031 |
| 2 | 3 | no tap | no tap | | | | | | | | |

*See also Figure 7
†Not all the fluid was aspirated when over 20 cc were present in the joint

with duration of effusion (Table V) The variations may actually all be related to varying severity, since the cases of longest duration of effusion or disease were in general the more severe cases

The protein concentration in a chronic effusion in rheumatoid arthritis may remain at essentially the same level over a period of months or years In one patient in whom 24 aspirations were made in 16 months, the total variation in protein concentration was from 3 6 to 4 4 gm per 100 cc, with the exception of one value of 4 9 gm obtained 2 days after the knee had been irrigated with 0 9 per cent saline solution Fluids from 4 consecutive taps in 1 month contained 3 9, 3 8, 3 9 and 3 8 gm of protein per 100 cc Several months after the above series of aspirations, the knee effusion disappeared entirely for 2 years but recurred when the patient had a generalized exacerbation of her arthritis It is of interest that the fluid at the time of the exacerbation had essentially the same content of protein as the original effusion, 4 0 gm per 100 cc Similar constancy of protein concentration in rheumatoid effusions of long duration has been seen in several other patients in whom repeated joint aspirations were made

In rheumatoid patients with intermittent effusions, on the other hand, fluctuations in the fluid protein concentration occurred, corresponding apparently with variations in the inflammatory reaction in the synovial tissues This was apparent in the patient described above who had bilateral knee effusions in regular cycles with peaks 6 days apart (Table IX) The unit concentration was greatest when the effusion first reappeared or was disappearing With increasing effusion the concentration decreased, suggesting that the entering liquid was slightly lower in protein than the fluid present in the joint With loss of fluid the protein concentration increased The contrasting findings in the case of mucin are significant The unit mucin concentration rose with increasing effusion, suggesting that the entering fluid carried a relatively high concentration of mucin The decreasing concentration of mucin as the effusion subsided would suggest that no new mucin was entering as the fluid was leaving and that the mucin present in the joint was being destroyed or removed

The total globulin fraction shows a greater correlation with etiology, severity and duration of the disease and duration of the effusion than the total protein or the albumin fraction In general,

creasing duration of disease and duration of effusion is apparent from Tables V and VIII and is probably related fundamentally to increased severity, as has been discussed above The highest globulin concentrations in this series occurred in effusions of over 1 year s duration in patients with severe rheumatoid arthritis The maximal globulin concentration in any other type of fluid was 3 0 gm per 100 cc, while 6 of 48 rheumatoid fluids showed concentrations above 3 0 gm, 1 being 6 77 gm per 100 cc Of the 6 effusions with high globulin content, 5 were of over 1 year s duration and represented 28 per cent of the 18 effusions of long duration that were analyzed In contrast, only 1 of 30 effusions of less than 1 year s duration (3 per cent) contained over 3 gm of globulin per 100 cc It is of interest that the 1 effusion of short duration with high globulin content occurred in a knee which had first been swollen and painful 2 years previously but had apparently been symptom free until 9 or 10 months before aspiration A similar, though less marked, increase in globulin with persistence of effusion was found in traumatic effusions The average globulin concentration in these fluids of less than 3 months duration was 0 80 gm per 100 cc, in contrast to 1 70 gm in the 1 effusion of over 1 year s duration The corresponding albumin/globulin ratios were 4 85 and 3 26

The chief factor determining the levels of albumin and globulin in joint effusions appears to be the degree of permeability of the synovial tissues There is no consistent relationship between the relative concentrations of these proteins in fluid and in serum In mild inflammation, the fluid protein tends to remain low (averaging 3 5 gm per 100 cc ) and the albumin/globulin ratio is high (above 2 0) With greater inflammation as in the majority of rheumatoid joints, the permeability is increased so that the fluid protein concentration rises and the ratio of albumin to globulin decreases, approaching that of the serum If effusions in rheumatoid arthritis persist for months or years the total protein content rises only slightly but the albumin/globulin ratio decreases markedly The fluid globulin concentration becomes approximately the same as that of the blood, while the fluid albumin remains only two thirds as high as the serum albumin Such high globulin concentrations suggest that the prolonged severe inflammation has led to changes in the tissues that make

fluids with relatively low total protein concentrations, such as traumatic effusions, have low globulin concentrations with albumin/globulin ratios ranging from 2 0 to 8 0 Apparently the relative impermeability of normal synovial tissues to globulin as compared with albumin is maintained even in the presence of the slightly increased permeability resulting from mild inflammation Further evidence of this differential permeability to individual protein fractions is found in the electrophoretic patterns of synovial fluid from traumatic arthritis In the 7 cases studied in this laboratory, the albumin was always higher in the fluid than in the serum, alpha-1 and beta-globulins were essentially the same in both and alpha 2 and gamma globulins were lower in the fluid [169] Schurch, Viollier and Sullmann[177] reported that the albumin/globulin ratios in traumatic fluids were the same as those of the corresponding sera but the concentration of alpha-2 globulin was lower in fluid than in serum Olhagen[141a] found the relative distribution of proteins in traumatic fluids about the same as in the plasma with slightly higher concentrations of albumin and gamma-globulin in the fluid With more severe inflammation, and consequently higher fluid protein concentrations, as in the majority of Group II fluids, the proportion of globulin in the entering protein increases, with the result that the albumin/globulin ratio falls below 2 0, occasionally below that of the serum This is explicable by the fact that the differential permeability to albumin and globulin does not persist when the membrane becomes easily permeable to proteins The loss of differential permeability is apparent in the electrophoretic patterns, which usually show essentially equal concentrations of albumin and gamma globulin in the fluid and serum The concentration of alpha 2 globulin remains lower in the fluid than in the serum

The relationship between the fluid globulin concentration and the severity of the joint involvement was apparent in effusions from gonococcal arthritis Fluids from which positive cultures were obtained had an average globulin content of 2 5 gm per 100 cc in contrast to 2 0 gm in those with negative cultures (Table IV) In rheumatoid effusions, also, increased globulin concentration was one of the most consistent evidences of greater severity of the joint disease (Table VII)

A tendency toward increasing globulin concentration with in

| GROUP II | | |
|---|---|---|
| Rheumatoid Arthritis | 42 | 58 |
| Probable Rheumatoid Arthritis | 13 | 13 |
| Reiter's Syndrome | 10 | 12 |
| Syphilitic Arthritis — Congenital | 7 | 9 |
| Tuberculous Arthritis | 4 | 4 |
| Gonorrheal Arthritis | 13 | 15 |
| Septic Arthritis | 8 | 8 |
| Meningococcal Arthritis | 1 | 1 |

4.47 6.77
4.69
3.62
‡

⊗ *fluids from traumatic* arthritis of more than 3 months duration

⊖ fluids from degenerative joint disease secondary *to other* joint abnormality

○ fluids from *rheumatoid arthritis* of mild severity

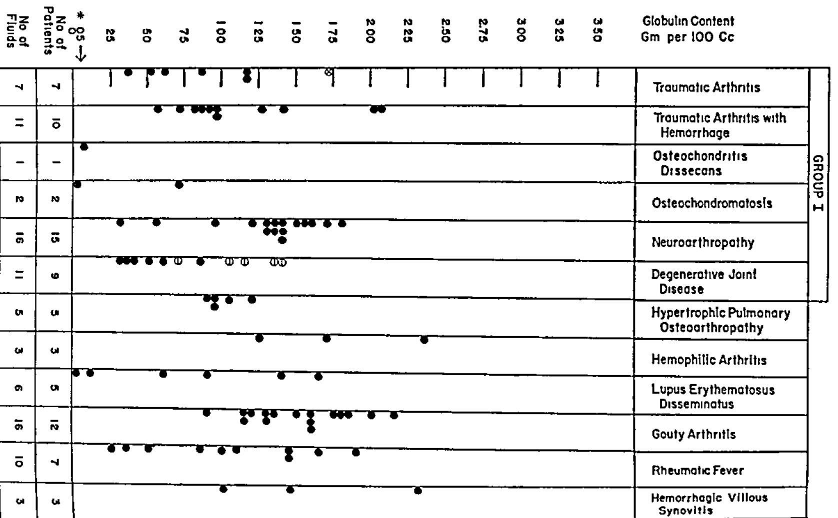
◐ fluids from rheumatoid arthritis of moderate severity

⊙ fluids with positive cultures

● fluids of the types *designated* by the headings, with the exception that the symbol *indicates in* traumatic arthritis fluids of less than 3 months *duration in degenerative* joint disease, primary degenerative joint *disease in* rheumatoid arthritis severe disease, and in the infectious arthritides, fluids with negative cultures

‡ a fluid from a *patient* with *severe* renal disease due to amyloidosis

Figure 10 Concentration of globulin in synovial fluid from various joint diseases The asterisk represents the value in one normal fluid



This increase in serum protein in rheumatoid arthritis is chiefly in the globulin fraction, which tends to rise steadily with duration of disease Only 12 of 33 cases of less than 1 year s duration had globulin contents over 3 00 gm per 100 cc in contrast to 39 of 57 cases of over 5 years' duration (Table VIII) Greater severity of the disease also tends to cause a higher level of globulin in the serum (Table VII) The average concentration in 34 mild cases was 2 7 gm per 100 cc compared with an average of 3 7 gm in 41 severe cases The average globulin fraction in the 163 cases of rheumatoid arthritis in which it was determined was 3.2 gm per 100 cc with a maximum of 7 10 and a minimum of 2 0 gm

Similar increases in serum total protein and globulin concentrations with increasing severity of rheumatoid arthritis have been found by other investigators The average globulin concentration in mild cases in Davis s[48] series was 2 8 gm per 100 cc compared with 3 9 gm in severe cases Scull, Bach and Pemberton[179] found that the globulin concentration was above 3 2 gm per 100 cc in 4 of 27 moderately severe cases in contrast to 30 of 48 severe cases Davison, Woolley and Donovan[49] reported a range of globulin concentrations from 0 4 to 2 9 gm per 100 cc in 8 clinically inactive cases as compared with a range from 0 3 to 5 1 in 43 active cases Wallis [04] also found a correlation between the globulin content of serum and the activity and extent of disease the globulin being above 3 0 gm in 11 of 19 cases with widespread involvement in contrast to 1 of 11 with slight or moderate involvement

Electrophoretic patterns of plasma or serum from patients with rheumatoid arthritis have shown that elevation of the concentration of globulin fractions and lowering of the albumin concentration have been associated consistently with activity of the disease With few exceptions both the alpha- and gamma globulin components have been increased in most series[53, 123, 127, 140, 141, 14, 148, 195, 196, 204] Apparently the first change is an increase in the alpha globulins, which may or may not persist, with a subsequent rise in the gamma globulin A decrease in albumin and an increase in alpha- or gamma-globulins were found in all but 3 of 36 cases[169] This group included many early and mild cases in which no alteration of albumin/globulin ratio was detectable by the Howe method

the removal of globulin (which is known to take place by way of the lymphatics[18]) even more difficult than it is normally

The electrophoretic patterns of synovial fluids corroborate the fact that the globulin fractions increase with greater severity of inflammation[169] In traumatic effusions, as stated above, the albumin is always higher in the fluid than in the serum and the globulin fractions are the same or lower in the fluid In 7 rheumatoid patients with early or mild involvement of the joint, 1 patient with gout, 1 with rheumatic fever, 1 with hypertrophic pulmonary osteoarthropathy and 2 with Reiter s syndrome, the electrophoretic pattern of the fluid resembled that of traumatic fluids The differences between the fluid and serum albumin levels, however, were not so great In cases of rheumatoid arthritis with greater severity of inflammation, the patterns showed the albumin concentration equal in the fluid and serum or lower in the fluid, and the gamma globulin higher in the fluid than in the serum[169] Schurch, Viollier and Sullmann[177] found similar changes in 1 patient with rheumatoid arthritis and 1 with tuberculous arthritis, and Olhagen[141a] reported remarkably high concentrations of gamma-globulin in rheumatoid fluids

The protein concentration of the serum of patients with rheumatoid arthritis increases with duration of disease but, as mentioned above, there is no exact correlation between protein changes in serum and fluid In the 172 patients studied in this laboratory, the protein concentration averaged 7 50 gm per 100 cc The minimal and maximal figures were 4 83 and 10 1 gm, but the majority of the values fell between 6 5 and 8 0 gm per 100 cc, corresponding in general with those found by other workers[6 48 49 166 179 197] The average concentration in rheumatoid arthritis of less than 1 year s duration was 7 3 gm per 100 cc in contrast to an average of 7 6 gm in cases of over 1 year s duration (Table VIII) Analysis of the individual figures shows that only 4 of 47 cases (8 5 per cent) of less than 1 year s duration had total proteins above 8 00 gm, while a significantly greater per cent, 32 of 127 cases (25 per cent), of more than 1 year s duration were above 8 00 gm, 1 being 10 1 gm A similar increase in serum protein with greater severity of disease was apparent The average concentration in mild cases was 7 4 gm per 100 cc, compared with 7 6 gm in severe cases

tion In many fluids from Group II, however, numerous small flecks of fibrin were present in the fluid when it was withdrawn

MUCIN AND VISCOSITY

The average concentration of mucin in normal human fluid in our series is 0 104 gm nitrogen per 100 cc with a variation from 0 068 to 0 135 gm nitrogen[171] Fisher[67] found 1 95 per cent of mucin, and Achard and Piettre[3] reported a concentration of 5 7 per cent The mucin-glucosamine concentration in our series varied from 050 to 132 gm per 100 cc, with an average of 087 Ragan and Meyer[158] found concentrations of hyaluronic acid varying from 0 04 to 0 33 mg per cc The average relative viscosity of the fluid in our series is 235 at 38° C, with a range from 5 7 to 1,160 Schneider[176] reported similar variation, from 3 9 to 1,490, Kling[113] found viscosities of 10 7 and 20 in 2 normal fluids, and Ragan and Meyer[158] reported viscosities from 2 3 to 575 Marked variations from one joint to another have been found by Panizza[145] and Davies[44] in animals

Changes in the concentration of mucin in joint disease are related to the type, severity and duration of the disease and the duration of the effusion In general, it may be said that the mucin content is low in fluids in which other signs of marked inflammation are present, namely, turbidity, high total leukocyte and polymorphonuclear counts, high total protein, high globulin and lowered sugar concentrations

The mucin concentration in synovial fluid varies in different joint diseases (Figure 11) In traumatic fluids, it tends to be the same per cubic centimeter as that of normal fluid in spite of a five to twenty five fold increase in the volume of fluid in the joint It is interesting to note that the unit concentration remains normal (0 001 gm nitrogen as mucin per cc) when the fluid is formed by diffusion, even though the swelling occurs rapidly, but is greatly reduced when the effusion is formed by hemorrhage with direct flow of blood into the joint This is in accord with the hypothesis that mucin is added to the dialysate of blood plasma as it diffuses through the tissues surrounding the joint Another possible explanation for the lower concentrations in hemorrhagic effusions would be the presence in the entering blood of an enzyme which could destroy mucin However, we have been unable

To summarize, the presence of a high concentration of protein in the fluid (above 5.5 gm. per 100 cc.), and especially of globulin (above 2.1 gm. per 100 cc.), indicates that the inflammatory reaction in the joint is not traumatic in origin. The synovial fluid protein concentration rises with increasing duration of self-limited effusions or with increasing severity of disease.

### FIBRINOGEN

Normal synovial fluid contains no fibrinogen.[171] Even in effusions, fibrinogen is seldom found in quantities large enough to be precipitable by the method of Cullen and Van Slyke.[42] It was determined in this way in only 6 fluids of the present series, 1 each from rheumatoid arthritis, rheumatoid arthritis (diagnosis probable), gonococcal arthritis, Reiter's syndrome, hypertrophic pulmonary osteoarthropathy and a case of malignant lymphoma of Hodgkin's type. Smaller amounts of fibrinogen, however, were found in many of the fluids, and could be estimated by the size of the clot formed.

The concentration of fibrinogen varies with the type and severity of the joint disease and the duration of the effusion. The majority of fluids of Group I do not clot, and even when clotting does occur, they never form large, firm clots immediately. In this series, fluids from patients with hypertrophic pulmonary osteoarthropathy, however, differed from those of Group I in this respect, since 4 of the 5 examined formed firm clots. The content of fibrinogen in the plasma in these 4 cases was markedly elevated (averaging 0.60 gm. per 100 cc.), whereas it was normal in traumatic cases (0.34 gm. per 100 cc.).

The majority of specific infectious and rheumatoid fluids coagulate, and in many cases rapidly form large, firm clots. The average concentration of fibrinogen in plasma corresponding to these Group II fluids was 0.53 gm. per 100 cc. In rheumatoid arthritis the concentration in synovial fluid is apparently inversely related to the duration of the effusion, as is shown in Table V. Rheumatoid fluids of more than 1 year's duration show less tendency to clot than those of shorter duration.

The possibility of a preformed clot which could not be withdrawn at aspiration was suspected in only 1 case, a patient with hemophilia who had been transfused a few hours before aspira

| | | | |
|---|---|---|---|
| GROUP II | Rheumatoid Arthritis | 94 | 125 |
| | Probable Rheumatoid Arthritis | 17 | 17 |
| | Reiters Syndrome | 9 | 11 |
| | Syphilitic Arthritis — Congenital | 8 | 9 |
| | Tuberculous Arthritis | 7 | 8 |
| | Gonorrheal Arthritis | 25 | 27 |
| | Septic Arthritis | 13 | 16 |
| | Meningococcal Arthritis | 2 | 2 |

- ⊗ fluids from traumatic arthritis of more than 3 months duration
- ⊖ fluids from degenerative joint disease secondary to other joint abnormality
- ○ fluids from rheumatoid arthritis of mild severity
- ◐ fluids from rheumatoid arthritis of moderate severity
- ⦶ fluids with positive cultures
- ● fluids of the types designated by the headings with the exception that the symbol indicates in traumatic arthritis fluids of less than 3 months duration in degenerative joint disease primary degenerative joint disease in rheumatoid arthritis, severe disease and in the infectious arthritides, fluids with negative cultures

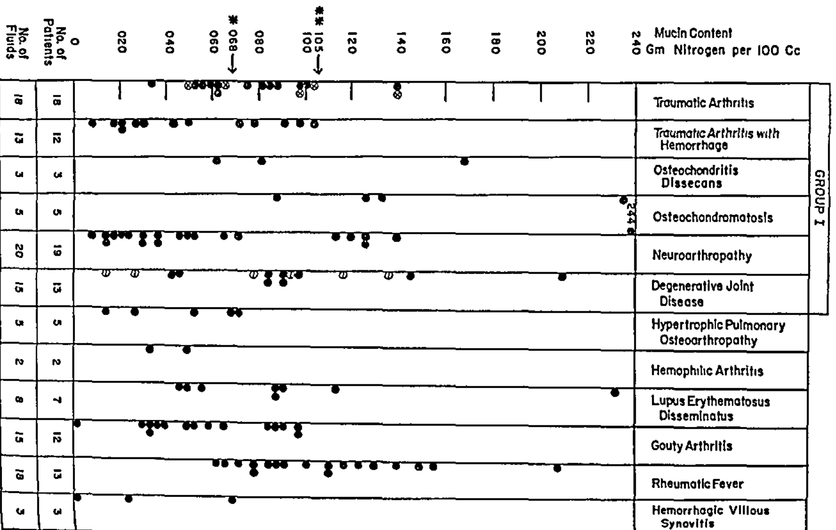



FIGURE 11 Concentration of mucin nitrogen in synovial fluid from various joint diseases The asterisks represent the minimum and maximum values in normal fluids

results either in accelerated production or retarded destruction of these mucins Attempts to demonstrate a destructive action of thyroxin on synovial mucin in vitro have not been successful From histochemical studies, Asboe-Hansen[7a] has concluded that hyaluronic acid is secreted by mast cells and that thyroid hormone regulates the amount of polysaccharide formed

Further suggestion of hormonal regulation of mucin metabolism has been given by observations on the effect of sex hormones Ogston, Philpot and Zuckerman[138] demonstrated that estrogenic stimulation produced not only an increase in the size of the con nective tissue cells but also a viscous, mucin containing exudate in the sexual skin of monkeys Bachman, Collip and Selye[8] showed that a more generalized edema, not involving the sexual skin, was produced if estriol injections were continued after the primary swelling of the sexual skin had appeared and subsided Hardesty[83] noted that the mucoid content of capons combs was greatly augmented by injection of male hormone and was also increased, though to a lesser extent, by female hormone Furthermore, the diminished spread of India ink in rabbits' skin after injection of estrone, demonstrated by Sprunt, McDearman and Raper,[191] again suggests that estrin increased intercellular mucin Loeb Suntzeff and Burns[122] observed an increase in the amount of fibrous hyaline tissue between the connective tissue cells in the vagina of mice after injection of estrogenic substances Apparently no evidence was obtained as to whether or not this increased intercellular tissue was mucin

A marked increase in viscosity is produced in some rheumatoid fluids by large doses of adrenocorticotrophic hormone or of cortisone, as discussed below The extent to which the normal activity of the pituitary or the adrenal cortex regulates the production and degree of polymerization of mucin cannot be determined from this evidence

Fluids of Group II have a lower average mucin concentration than traumatic fluids The concentration tends to decrease with increasing severity, the lowest values being found in severe cases of specific infectious or rheumatoid arthritis Twelve fluids (2 from severe cases of rheumatoid arthritis, 1 from a case with probable rheumatoid arthritis and 9 from specific infectious arthritis due to hemolytic streptococci staphylococci or gonococci)

to demonstrate such an enzyme in normal blood or even in blood from patients with rheumatoid or other types of arthritis

Exceptionally high concentrations of mucin were found in many fluids from Charcot joints and in fluids from lupus erythematosus disseminatus, degenerative joint disease and osteochondromatosis A fluid obtained post mortem from a knee which showed extreme degenerative changes but did not contain an abnormal amount of fluid had one of the highest concentrations in this series (0 208 gm nitrogen per 100 cc ) The highest concentrations of all were found in cases of osteochondromatosis, in which the average (0 166 gm nitrogen per 100 cc ) was much higher than that of normal human fluid (0 104 gm ) The significance of extremely high mucin concentrations is not clear It is probable that they are due to increased formation of mucin in response to tissue stimulation without the increased destruction of mucin usually associated with marked inflammation of joints Comparison of the viscosity estimated from the mucin-glucosamine content (see p 62 and Figure 3) with the observed viscosity of fluids from neuroarthropathy, lupus, degenerative joint disease and osteochondromatosis supports this hypothesis and indicates that the mucin is not degraded That stimulation of synovial cells with increased production of mucin can be caused by trauma is indicated by King's[110] observations in acute and chronic inflammation of traumatic origin He demonstrated enlargement of the Golgi apparatus of the synovial cells and accumulation of intercellular mucoid material (Unfortunately, the mucin concentrations of the fluids were not determined ) There is also the possibility that the high *mucin concentration arises in part* from destruction of normal cartilage or chondromata However, the presence of synovial polysaccharide in cartilage has not been demonstrated by chemical or immunological means [210]

An abnormally high concentration of mucin was found also in the synovial fluid from a myxedematous patient This suggests that the metabolism of synovial fluid mucin and that of the mucin of subcutaneous tissue undergo comparable changes when thyroid activity is reduced * A decrease in thyroid activity apparently

*Connective tissue mucin from normal and myxedematous animals has been shown to be similar to synovial mucin by physical characteristics and by enzymatic reactions in vitro [218]

mucin either alone or associated with incomplete synthesis Attempts to demonstrate the presence of mucinase or a similar enzyme in such fluids have not been successful [131, 170] It has been shown, however, that ascorbic acid hydrogen peroxide and serum with high alkaline phosphatase activity both cause depolymerization of synovial fluid mucin in vitro It is possible that abnormality in the metabolism of one of these substances may in some cases explain the destruction of mucin in pathological fluids Lutwak-Mann[1--] found no ascorbic acid in normal synovial fluid, but in our series the synovial fluid from one patient with rheumatoid arthritis contained 1 1 mg per 100 cc An inverse relationship has been demonstrated between the alkaline phosphatase activity and the viscosity of synovial fluid (see p 77)

The findings in Group II fluids indicate that mucin destruction is more rapid than normal in many cases However, the breakdown probably represents merely a splitting of the macromolecules No free glucosamine, one of the hydrolytic products, is present even in the fluid from the most severe cases, showing that complete breakdown of the polysaccharide does not take place Whether the change in mucin is identical in all types of Group II fluids cannot be determined from the available evidence In infectious arthritis, the initial fluid, even from severe cases, usually contains fairly normal mucin that precipitates in a ropy clump Subsequently, the fluid becomes less viscous and the mucin precipitate becomes smaller and less cohesive In effusions in rheumatoid arthritis, on the other hand, the mucin precipitate is usually friable with a cloudy solution even early in the disease, except in very mild or atypical cases

The nature of the precipitate obtained with acetic acid and the viscosity of the fluid give the best indication of the state of the mucin in any pathological fluid However, a method that may prove to be of value in estimating the degree of mucin degradation is a comparison of the relation between the viscosity of the fluid and the mucin concentration with the similar relationship for normal cattle fluid (Figure 3) The empirical proportionality between the logarithm of the viscosity and the concentration of mucin glucosamine is apparently unaffected by the particular solvent or the state of the polysaccharide (Figure 3), even though these cause changes in the viscosity per unit of glucosamine The

showed only slight haziness on precipitation with acetic acid, indicating merely a trace of mucin

Of more significance than the changes in concentration are the alterations in the characteristics of mucin in pathological fluids Normal fluid has a viscosity ranging from 5 7 to 1,160, with an average of 235 at 38° C The mucin from such fluid is precipitated by acetic acid as a tough, ropy mass, and the surrounding solution is clear (Figure 13a) The changes in joint disease consist of reduction in viscosity and loss of characteristic precipitability with acetic acid and are similar to those produced by the in vitro depolymerization of mucin by ascorbic acid hydrogen peroxide or by bacterial or tissue enzymes * The abnormalities are greater in the fluids of Group II than in those of Group I and increase, in general, proportionally with increasing severity (Figure 12 and the chart at the back of the book)

Traumatic arthritis fluids, for example, show normal unit concentration of mucin but viscosity reduced from the normal range to an average of 31 at 38° C with minimal maximal values of 8 4 and 83 The precipitability of mucin, however, remains fairly normal, i e, the addition of acetic acid to a final concentration of 1 per cent causes the characteristic ropy precipitation with surrounding solution that is clear (See Figure 13a ) In specific infectious and rheumatoid fluids, on the other hand, the viscosity tends to be much lower, with averages of 14 6 and 13 1 respectively The precipitability shows even more marked alteration than the viscosity When there is relatively little change from normal, the mucin is precipitated in a clump, but this is soft and friable and the solution is cloudy (Figures 13b and 13c) In the fluids with more abnormal mucin, a flocculent or slightly fibrous precipitate is obtained and the surrounding solution is very cloudy (Figure 13d) In extreme cases, no definite precipitate is formed, the solution becoming only slightly cloudy

The similarity of these changes to those produced by enzymatic digestion of mucin suggests that the reduced concentration of mucin in Group II fluids is caused by increased destruction of

*Synovial fluid mucin can be depolymerized in vitro by three types of substances bacterial or tissue enzymes serum with high alkaline phosphatase activity and ascorbic acid hydrogen peroxide (See reviews of the subject[79, 131, 170]) Further breakdown with hydrolysis of the polysaccharide and liberation of reducing sugars and glucosamine is caused by the bacterial enzymes

| GROUP II | | |
|---|---|---|
| Rheumatoid Arthritis | 63 | 69 |
| Probable Rheumatoid Arthritis | 28 | 28 |
| Reiter's Syndrome | 16 | 20 |
| Syphilitic Arthritis — Congenital | 9 | 11 |
| Tuberculous Arthritis | 11 | 11 |
| Gonorrheal Arthritis | 7 | 7 |
| Septic Arthritis | 9 | 9 |
| Meningococcal Arthritis | 8 | 14 |

- ⊗ fluids from traumatic arthritis of more than 3 months duration
- ⊖ fluids from degenerative joint disease secondary to other joint abnormality
- ○ fluids from rheumatoid arthritis of mild severity
- ◐ fluids from rheumatoid arthritis of moderate severity
- ⊖ fluids with positive cultures
- ● fluids of the types designated by the headings, with the exception that the symbol indicates in traumatic arthritis, fluids of less than 3 months duration in degenerative joint disease, primary degenerative joint disease in rheumatoid arthritis, severe disease and in the infectious arthritides, fluids with negative cultures

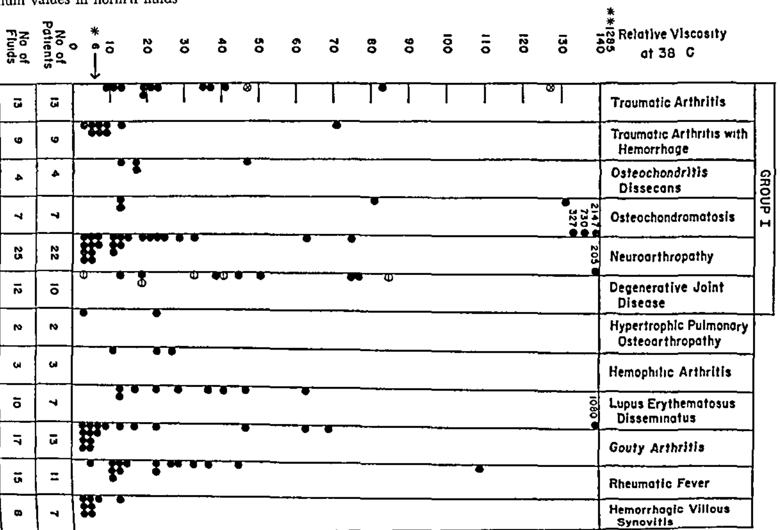
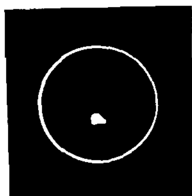



FIGURE 12 Relative viscosity at 38 C of synovial fluid from various joint diseases The asterisks represent the minimum and maximum values in normal fluids



a



b



c



d

FIGURE 13 Types of mucin precipitate obtained with acetic acid (the beakers containing the mucin were placed on a black surface and the photographs were taken from above)

a Tight ropy clump in a clear solution
b Soft mass in a very slightly cloudy solution
c Small friable masses in a cloudy solution
d Few flecks in a cloudy solution

mucin glucosamine concentration of any fluid can, therefore, be extrapolated to the concentration chosen as a basis of comparison (7.5[2] mg. of glucosamine per 100 cc.) and the corresponding viscosity compared with that found for normal fluid at this standard glucosamine concentration. For example, if a fluid has a mucin glucosamine concentration of 8.2[2] mg. per 100 cc. and a relative viscosity at 38° C. of 16.6, extrapolation (using Figure 3) to a concentration of 7.5[2] mg. per 100 cc. gives a viscosity of 11 in contrast to the value of 50 found in normal cattle fluid at this concentration. The disproportion between viscosity and mucin content is most marked in those fluids in which the type of precipitate obtained with acetic acid is indicative of the greatest breakdown of mucin. However, even traumatic fluids, from which the mucin is precipitated normally, show lower viscosities than would be expected from the mucin concentration, suggesting that the first stage of mucin breakdown (presumably a partial splitting of the long chain molecule) has taken place. The degree of degradation of mucin in such fluids is apparently comparable to that produced by any of the usual methods of preparing mucin from normal fluid. The viscosity of solutions of mucin prepared by these methods is lower in proportion to the concentration than was that of the normal fluid from which it was obtained (Figure 3).

The nitrogen/glucosamine ratio of the mucin precipitated by acetic acid from joint fluid is also indicative of the state of the mucin. With increasing breakdown of the polysaccharide, the ratio decreases from the normal of 1.5. In general, estimates of the degree of mucin degradation provided by this method, by the relative viscosity of the fluid and by the type of mucin precipitate agree fairly well (Table X).

A reversal of the changes in mucin with improvement in the joint disease was apparent in this series in cases in which repeated aspirations were done. In one patient with rheumatic fever, the synovial fluid withdrawn 12 hours after onset of an effusion contained 0.08 gm. nitrogen as mucin per 100 cc., while fluid from the same knee 3 days later had a mucin nitrogen content of 0.15 gm. per 100 cc. The change paralleled a drop in the fluid leukocyte count from 13,800 to 1,980 cells per cu. mm. Similarly, fluid from a septic joint (*Staphylococcus aureus*) had no precipitable mucin 5 days after onset of the arthritis but showed a definite

TABLE X Comparison of Different Methods of Estimating the Concentration and State of Mucin in Various Types of Joint Disease*

| | Relative viscosity at 38 C | Mucin nitrogen gm /100 cc | Mucin glucosamine gm /100 cc | Type of mucin ppt † | Mucin nitrogen / Glucosamine |
|---|---|---|---|---|---|
| Tuberculous arthritis | 7 7 | 011 | 026 | P | 0 80 |
| Reiter s syndrome | 10 5 | 067 | 052 | P | 1 38 |
| Rheumatoid arthritis | 11 0 | 067 | 040 | P | 1 38 |
| Syphilitic arthritis | 11 4 | 058 | 039 | P | 1 12 |
| Infectious arthritis‡ | 13 7 | 058 | 047 | P | 1 56 |
| Pulmonary osteoarthropathy | 15 3 | 047 | 037 | P | 1 10 |
| Gouty arthritis | 17 0 | 058 | 040 | P | 1 03 |
| Hemophilia | 21 0 | 041 | | P | |
| Rheumatic fever | 22 0 | 108 | 093 | G | 1 52 |
| Probable rheumatoid arthritis | 24 0 | 068 | 048 | F | 1 44 |
| Neuroarthropathy | 31 0 | 068 | 046 | F | 1 38 |
| Traumatic arthritis | 31 0 | 080 | 098 | G | 0 56 |
| Degenerative joint disease | 41 0 | 090 | 080 | G | 0 94 |
| Lupus erythematosus disseminatus | 149 0 | 092 | 059 | G | 1 37 |
| Normal human knee joints§ | 235 0 | 104 | 087 | G | 1 16 |
| Myxedema | 361 0‖ | 192‖ | | G | |
| Osteochondromatosis | 499 0 | 166 | 099‖ | G | 1 41‖ |

*Arranged in order of increasing viscosity not all the columns contain equal numbers of fluids
†The type of precipitate is expressed in symbols having the following significance P=small friable masses in a cloudy solution F=soft mass in a clear or slightly cloudy solution G=tight ropy clump in a clear solution (See Figure 13 )
‡Includes streptococcal staphylococcal pneumococcal *F coli* gonococcal and meningococcal arthritis
§These fluids were obtained post mortem
‖Results based on the analysis of only 1 fluid

precipitate 3 days later when the total cell count had fallen from 151,500 to 90 000 cells per cu mm Gradual improvement was found also in a case of rheumatoid arthritis The fluid aspirated 4 weeks after the onset of the effusion contained 0 06 gm nitrogen as mucin per 100 cc One week later the fluid contained 0 09 gm , and 5 months after onset the content was 0 12 gm The corresponding improvement in the activity of the disease was reflected in the drop in corrected sedimentation rate from 1 07 mm per minute to 0 82 and finally to 0 69

Administration of adrenocorticotrophic hormone or of cortisone to rheumatoid patients resulted in a dramatic improvement in the state of synovial mucin as determined by viscosity of the fluid and type of mucin precipitate In one patient the viscosity rose from 18 to 6,080 following 110 days of ACTH treatment Whether this change represents inactivation of an enzyme that causes degradation of mucin or activation of an enzyme capable

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| Tuberculous arthritis | 7 7 | 044 | 026 | P | 0 80 |
| Reiter s syndrome | 10 5 | 067 | 052 | P | 1 38 |
| Rheumatoid arthritis | 11 0 | 067 | 040 | P | 1 38 |
| Syphilitic arthritis | 11 4 | 058 | 039 | P | 1 12 |
| Infectious arthritis‡ | 13 7 | 058 | 047 | P | 1 56 |
| Pulmonary osteoarthropathy | 15 3 | 047 | 037 | F | 1 10 |
| Gouty arthritis | 17 0 | 058 | 040 | P | 1 03 |
| Hemophilia | 21 0 | 041 | | P | |
| Rheumatic fever | 22 0 | 108 | 093 | G | 1 52 |
| Probable rheumatoid arthritis | 24 0 | 068 | 048 | F | 1 44 |
| Neuroarthropathy | 31 0 | 068 | 046 | F | 1 38 |
| Traumatic arthritis | 31 0 | 080 | 098 | G | 0 56 |
| Degenerative joint disease | 41 0 | 090 | 080 | G | 0 94 |
| Lupus erythematosus disseminatus | 149 0 | 092 | 059 | G | 1 37 |
| Normal human knee joints§ | 235 0 | 104 | 087 | G | 1 16 |
| Myxedema | 361 0‖ | 192‖ | | G | |
| Osteochondromatosis | 499 0 | 166 | 099‖ | G | 1 41‖ |

*Arranged in order of increasing viscos ty not all the columns contain equal numbers of fluids
†The type of precipitate is expressed in symbols having the following significance P=small friable masses in a cloudy solution F=soft mass in a clear or slightly cloudy solution G=tight ropy clump in a clear solution (See Figure 13 )
‡Includes streptococcal staphylococcal pneumococcal *E coli* gonococcal and meningococcal arthritis
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of synthesizing highly polymerized mucin or is unrelated to enzyme activity is not known

To summarize, definite breakdown of the mucin in a fluid (evidenced by a friable precipitate and cloudy solution on addition of acetic acid) indicates that the effusion is probably not traumatic (Group I) in origin The degree of destruction of mucin can be estimated best by the nature of the precipitate obtained with acetic acid and is also indicated by the relative viscosity of the fluid Unusually high concentrations of undegraded mucin are found in lupus erythematosus disseminatus, degenerative joint disease and osteochondromatosis

## NON ELECTROLYTES

### *Non protein Nitrogen and Uric Acid*

The synovial fluid concentration of non electrolytes that are readily diffusible and not rapidly utilized in the joint (such as non protein nitrogen and uric acid) is dependent on the plasma concentration and is not of diagnostic value In effusions of all types the concentration is approximately equal in fluid and plasma as is found normally and as would be expected from the fact that the synovial tissues are readily permeable to these substances Similar distribution has been reported by other workers[7 30 31 39 104]

Equal distribution of uric acid between blood and fluid was found in all effusions even in gout The duration of the gouty effusions varied from 10 hours to 10 weeks (see table, p 65) These findings do not support Kling's thesis[115] that the concentration of uric acid in the fluid is significantly higher than that of the blood during an acute attack of gout

### *Bilirubin*

Bilirubin also diffuses readily from plasma to fluid in jaundiced patients, as was noted by Kling[115] In a patient with gout and jaundice Burman[76] found an icteric index of 17 compared with a value of 21 in the blood 2 days later In 1 fluid in our series, obtained post mortem from a jaundiced patient who had had no evidence of joint disease the icteric index determined in this laboratory was 20 as compared with 75 in the serum

Uric Acid Concentration in Gouty Effusions

| Duration of effusion | Se mg./100 cc | Fl mg./100 cc |
|---|---|---|
| 10 hours | 12 5 | 12 6 |
| 36–48 hours | 5 4 | 6 0 |
| 1 week | 6 3 | 6 1 |
| 1 week | 6 7 | 6 6 |
| 10 days | 4 2 | 4 6 |
| 10 days | 4 2 | 4 6 |
| 3 weeks | 7 5 | 7 2 |
| 4 weeks | 3 9 | 3 8 |
| 5 weeks | 9 6 | 9 9 |
| 5 weeks | 9 6 | 9 5 |
| 10 weeks | 8 4 | 8 9 |

*Sulfonamides*

Similarly, the synovial tissues are readily permeable to sulfanilamide After intravenous injection, prontosil appeared in the fluid in 9 minutes The synovial fluids from 3 cases of gonococcal arthritis contained 6 0, 5 4 and 7 8 mg of sulfanilamide per 100 cc after 2 days of treatment, in contrast to 4 6, 5 1 and 6 6 mg per 100 cc in the serum Keefer and Rantz[105] found approximately the same concentration of sulfanilamide in blood and fluid in 5 of 6 cases of gonococcal arthritis In 1 other case the concentration was much higher in the fluid (18 8 mg per 100 cc ) than in the blood (6 2 mg ) Of two patients in the present series treated with sulfathiazole, 1 showed essentially equal concentrations of the sulfonamide in serum and fluid (3 2 and 3 5 mg per 100 cc ), while the other had only a trace of sulfathiazole in the fluid when the serum concentration was 4 1 mg per 100 cc

*Penicillin*

Permeability of the synovial tissue to penicillin has been demonstrated by several investigators [9, 76, 94, 124, 187] Many have found the concentrations in the fluids to be comparable to those in the blood after intramuscular administration In other studies [22, 85, 86, 143] lower levels were found in the joint fluid after intramuscular injection Penicillin was found to remain in the fluid longer than in the blood [9, 86, 98]

*Chloromycetin*

Diffusion of chloromycetin from blood to synovial fluid was ap-

TABLE XI Concentrations of Glucose in Synovial Fluids Aspirated 3 to 4 Hours After Eating

| Case no | Hours after eating | Sugar mg per 100 cc Fluid | Blood | Difference |
|---|---|---|---|---|
| 1 | 4 | 102 | 81 | 21 |
| | | 103 | 81 | 22 |
| 2 | 4 | 101 | 96 | 5 |
| 3 | 3½ | 139 | 117 | 22 |
| 4 | 3 | 99 | 67 | 32 |
| 5 | 4½ | 98 | 75 | 23 |

parent in 1 patient with staphylococcal arthritis in our series The concentration in the fluid was greater than 16 but less than 64 mg per cc compared with a serum level greater than 32 but less than 128 mg per cc

*Sugar*

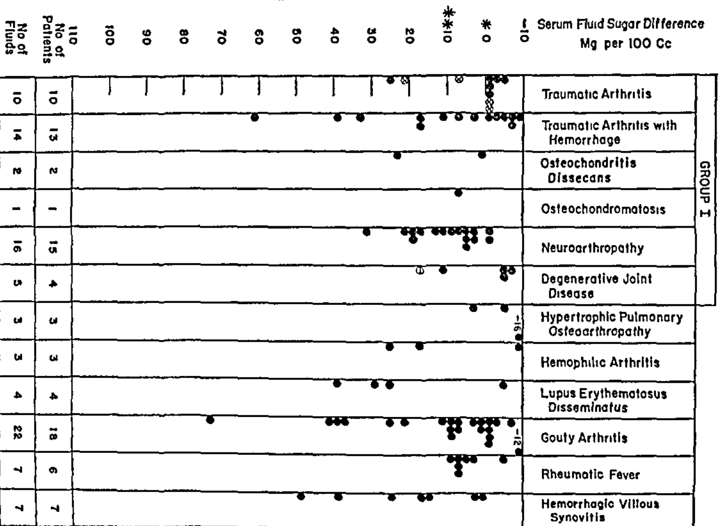
Variations in the concentration of sugar, in contrast to those with other non electrolytes, are of diagnostic significance* (Figure 14) The concentration of glucose in fluids of Group I in general is essentially normal, averaging less than 10 mg below that of the serum In many instances the fluid values are equal to those of the sera indicating that the rate of utilization by the cells of synovial tissues, cartilage and fluid is approximately equal to the difference between the rate at which glucose is supplied and the rate of removal In this series hemorrhagic effusions had lower concentrations of sugar than other traumatic fluids, the average level being 22 mg below that of the serum The increased glucolytic enzyme activity associated with the large amount of blood in the joint presumably causes this decrease in glucose

*It should be mentioned in connection with sugar levels that determinations of the concentration in fluids taken while patients are under anesthesia or within 3 to 4 hours after eating are seldom of diagnostic value The rise in blood sugar caused by anesthesia or ingestion of food is reflected in the fluid sugar and the relationship between the blood and fluid sugars varies markedly during the rise and fall of the blood sugar It has been shown that increase in the level of glucose in the blood is not usually reflected in the fluid of normal[100] or rheumatoid[214] joints for approximately 20 minutes The fluid sugar then rises slowly and steadily Later when the blood sugar falls rapidly the rate of utilization of sugar by the articular tissues and the rate of diffusion from the joint fluid back to the capillaries are not sufficiently rapid to keep the fluid sugar at or below that of the blood[100] As a result fluids withdrawn 3 to 4 hours after eating tend to have higher concentrations of glucose than blood taken at the same time (Table XI)

Fluids in Group II have a lower average glucose content than normal and Group I fluids The lowest values in this series (except some in fluids from severe rheumatoid arthritis of very long duration) occurred in the fluids in which organisms were found The reduction of the sugar concentration that occurred when there was a sufficiently large number of organisms to give a positive culture and a marked cellular response was particularly well shown in fluids from gonococcal arthritis The average sugar content of fluids from which no organisms could be grown was 83 mg per 100 cc, while the average for fluids with positive cultures was 29 mg (Table IV)

In rheumatoid effusions, sugar, like other components, shows a wide range in concentration The minimal and maximal values in this series were 0 and 132 mg per 100 cc There was a general tendency for the fluid level to be lower in severe and moderate than in mild cases (see Table VII) A correlation between duration of effusion and concentration was also shown the average being 78 mg per 100 cc in those of 6 weeks or less in contrast to 58 mg per 100 cc in those of over 1 year s duration (Table V) Furthermore all rheumatoid effusions that contained no sugar were of over 6 months duration

The decreased concentration of sugar is due in part to the decreased rate of entrance which has been shown to occur in the effusions of rheumatoid and infectious arthritis [213] This disturbs the normal equilibrium between entrance and utilization The reduced supply of glucose, associated presumably with increased utilization by inflamed and proliferated synovial tissues and by an increased number of leukocytes and by organisms if present, results in a marked lowering of the sugar level The cause of the difficulty in entrance of sugar into chronic effusions in rheumatoid arthritis and the similar delay in infectious arthritis is not known The reduction in the rate of entrance varies from patient to patient, depending apparently chiefly on the severity of the disease [213] It is not due to a reduction of capillary permeability" presumably, since the rate of entrance of such substances as proteins and lipoids is increased in the same joints Whatever the mechanism, it is probably merely a retardation of the usual mode of entrance of glucose for in normal calves the passage of glucose from blood to fluid is slower than that of thiocyanate [209]




| Disease | No of Patients | No of Fluids |
|---|---|---|
| Traumatic Arthritis | 10 | 10 |
| Traumatic Arthritis with Hemorrhage | 13 | 14 |
| Osteochondritis Dissecans | 2 | 2 |
| Osteochondromatosis | 1 | 1 |
| Neuroarthropathy | 15 | 16 |
| Degenerative Joint Disease | 4 | 5 |
| Hypertrophic Pulmonary Osteoarthropathy | 3 | 3 |
| Hemophilic Arthritis | 3 | 3 |
| Lupus Erythematosus Disseminatus | 4 | 4 |
| Gouty Arthritis | 18 | 22 |
| Rheumatic Fever | 6 | 7 |
| Hemorrhagic Villous Synovitis | 7 | 7 |

FIGURE 14 The difference between the concentrations of glucose in serum and synovial fluid in various joint diseases In the few cases in which *serum* glucose levels were not determined, an estimated concentration of 90 mg per 100 cc was used to calculate the serum fluid difference The asterisks represent the minimum and maximum values in normal fluids

| GROUP II | | |
| --- | --- | --- |
| Rheumatoid Arthritis | 87 | 111 |
| Probable Rheumatoid Arthritis | 32 | 32 |
| Reiter's Syndrome | 16 | 21 |
| Syphilitic Arthritis—Congenital | 8 | 10 |
| Tuberculous Arthritis | 22 | 24 |
| Gonorrheal Arthritis | 29 | 30 |
| Septic Arthritis | 27 | 28 |
| Meningococcal Arthritis | 11 | 15 |

⊗ fluids from traumatic arthritis of more than 3 months duration

⊖ fluids from degenerative joint disease secondary to other joint abnormality

○ fluids from rheumatoid arthritis of mild severity

◐ fluids from rheumatoid arthritis of moderate severity

⊕ fluids with positive cultures

● fluids of the types designated by the headings with the exception that the symbol indicates in traumatic arthritis, fluids of less than 3 months duration in degenerative joint disease, primary degenerative joint disease in rheumatoid arthritis severe disease and in the infectious arthritides, fluids with negative cultures

No exact correlation between the glucose level and total nucleated cell count was found in any type of fluid. This corroborates the conclusions of Collins,[39] who did not find the absolute correlation suggested by Cajori and Pemberton.[31] In many cases in our series, marked elevation of the white count caused no definite lowering of the sugar. For example, rheumatoid fluids with total counts of 33,100, 39,300 and 51,000 had sugar concentrations of 64, 68 and 61 respectively, while the entire group of rheumatoid fluids which had an average count of 14 052, had an average sugar concentration of 63. There were only two consistent relationships: no fluid with a total count above 20,000 had a sugar level equal to that of the serum, and there was a tendency for the fluid sugar to be markedly decreased (usually below 50) when the total count was above 40 000. Even in these cases the correlation was not exact and it was apparent that factors other than the total leukocyte count were of more importance in determining the glucose level in the fluid.

An apparent reciprocal relationship between fluid sugar and total leukocyte count would be expected since both changes are presumably evidences of increased inflammation and since it has been shown that leukocytes cause breakdown of glucose.[31, 121, 213] This apparent correlation and the relation to the severity of the inflammation are shown in the case of the patient with rheumatoid arthritis who had bilateral effusions that appeared and disappeared in regular cycles (Figure 7). During the period of increasing inflammation and effusion, the total leukocyte and absolute polymorphonuclear counts rose, while the sugar concentration fell. Subsequently, with decreasing inflammation, the counts fell and the sugar content increased. The decrease in the difference between serum and fluid glucose levels in some rheumatoid patients receiving adrenocorticotrophic hormone or cortisone gives further indication of the relationship of the sugar content of the fluid to the degree of inflammation of the synovial tissues.

The glucose level in the synovial fluid is affected by increased articular pressure but these sugar changes are not of diagnostic or prognostic significance. The significant level for diagnosis is that found on a second aspiration when intra articular pressure is lower. The effect of pressure was shown in 4 cases of rheumatoid

TABLE XII The Relationship of Intra articular Pressure and Concentration of Glucose in Synovial Fluid

| Case no and date | Initial pressure mm of synovial fluid | Leukocytes of synovial fluid per cu mm | Polymorpho nuclears per cent | Sugar mg per 100 cc Blood | Sugar mg per 100 cc Synovial fluid |
|---|---|---|---|---|---|
| Case 1 | | | | | |
| 12/20/38 | 220 | 9 600 | 57 | 91 | 7 |
| 1/14/39 | 120 | 9 900 | 42 | 91 | 81 |
| Case 2 | | | | | |
| 12/30/37 | over 700 | 12 100 | 80 | | 27 |
| 1/11/38 | 546 | 25 000 | 94 | | 59 |
| Case 3 | | | | | |
| 3/24/38 | 700 | 19 600 | 90 | | 20 |
| 4/ 1/38 | 170 | | | 107 | 72 |
| Case 4 | | | | | |
| 11/20/37 | over 700 | 11 800 | 87 | 89 | 11 |
| 12/ 1/37 | 0 | 30 700 | 78 | 73 | 75 |
| Case 5 | | | | | |
| 10/21/39 | over 700 | 15 600 | 76 | 99 | 55 |
| 10/26/39 | 100 | 7 480 | 49 | | 104 |

arthritis that had low glucose concentrations and high intra-articular pressures in the original fluids Aspirations were repeated within a short period of time, and a rise in glucose concentration coincident with a fall in pressure occurred in each case (see Table XII) The rapid rise in sugar, with no known change except reduction of intra-articular pressure suggests that the low sugar concentrations in the initial fluids might be due to decreased diffusing surface caused by compression of blood vessels by the high intra articular pressure The pressure of 700 mm of water found in 3 of the joint fluids is much higher than the pressure usually thought to occur in capillaries (approximately 400 mm of water) However, in 1 case (Case 1, Table XII) in which exceptionally marked proliferation of the synovial tissues was subsequently found at operation a fluid pressure of only 220 mm was apparently sufficient to cause reduction of sugar concentration The mechanism by which high intra articular pressure lowers the sugar content of fluid remains unexplained

Twenty one fluids obtained from patients with various joint diseases who had been fasting for 12 hours (or more) showed sugar concentrations more than 6 mg higher than the bloods taken at the same time It seems unlikely that such long periods would be necessary for the restoration of equilibrium All of the

reducing substances in the fluid were found to be fermentable by yeast The relatively high concentration of sugar in the fluid compared with that in the blood is difficult to explain

The above survey of the concentrations found in fluids from various joint diseases indicates that a low or absent sugar is not necessarily an indication of bacterial invasion of a fluid as Collins[39] presumed it to be In rheumatoid arthritis, persistently low sugar levels are an indication of severe or long continued disease Since the sugar content of synovial fluid is determined by the etiology and severity of the synovial inflammation, it is often of diagnostic and prognostic value If the sugar of a non hemorrhagic fluid is more than 20 mg per 100 cc below the blood level, the effusion is presumably not traumatic in origin In infectious arthritis the fluid sugar concentration can be used as one indication of the course of the synovitis and thereby aid in prognosis

*Lactate*

The concentration of lactate in normal human synovial fluid has not been determined In 6 normal cattle fluids the level ranged between 18 and 34 mg per 100 cc (The corresponding serum levels varied from 35 to 114 mg per 100 cc, the great variation resulting probably from the fact that the animals struggled before death )

The fluid lactate concentration in joint diseases varies with the etiology and severity In the 3 Group I fluids (obtained from Charcot joints) in which the lactate content was determined, the level in the fluid averaged essentially the same as that in the serum (13 mg per 100 cc as compared with 15 mg per 100 cc ) The concentration varied greatly in Group II fluids In 13 cases (1 rheumatic fever, 2 congenital syphilis 1 Reiter s syndrome, 1 meningococcal arthritis 1 gonococcal arthritis and 7 rheumatoid arthritis), the fluid lactate level was within 10 mg per 100 cc of the serum level The differences were much greater in the other 23 Group II fluids the fluid level usually being higher than the serum The greatest differences found were in a patient with tuberculous arthritis and in one with severe gouty arthritis in whom the fluid values were 79 and 97 mg per 100 cc and the serum values 16 and 22 mg per 100 cc respectively Fluid aspirated at the same time from an effusion in the other knee of

TABLE XIII Distribution Ratios for Chloride Calcium and Phosphorus in Various Diseases

| Case no. | Disease | $\frac{Cl_s}{Cl_f}$ | $\sqrt{\frac{Ca_f}{Ca_s}}$ | $\frac{P}{P_f}$ | Theoretical Donnan ratio |
|---|---|---|---|---|---|
| 1 | Normal | 98 | 87 | | 93 |
| 2 | Traumatic arthritis | | 91 | | 96 |
| 3 | Traumatic arthritis | 1 00 | | | 97 |
| 4 | Traumatic arthritis | 1 05 | | | 97 |
| 5 | Degenerative joint disease | 1 01 | 92 | 1 05 | 96 |
| 6 | Rheumatoid arthritis | 1 02 | 93 | 1 10 | 97 |
| 7 | Tuberculous arthritis | 1 02 | 90 | 99 | 97 |
| 8 | Septic arthritis | 98 | 97 | 1 09 | 98 |
| 9 | Septic arthritis | 98 | 94 | 1 00 | 98 |

the patient with gout, contained only 51 mg of lactate per 100 cc

In general, the lactate concentration in the fluid showed an inverse relationship to the sugar content (Figure 15) The significance of the relationship is not apparent, but possibly the increased lactate concentration is associated with greater utilization of glucose

ELECTROLYTES

The concentration of chloride is higher in normal human synovial fluid than in the serum, while the reverse is true of calcium The concentration of total inorganic phosphate is practically the same in fluid and serum [171] The distribution ratios are such as would be expected from the Donnan theory of equilibrium across a semipermeable membrane and from comparison with the distribution ratios for dialysates of blood plasma[167] (Table II) In the types of pathological fluid analyzed, the distribution of chloride, phosphate and calcium ions between serum and fluid varied slightly from case to case but there was no apparent correlation with the etiology, severity or duration The distribution ratios maintained essentially the same relationship to the theoretical Donnan ratios as found in normal fluid The chloride and phosphate concentrations per 100 cc of water were approximately equal in fluid and serum, although there was a slight tendency for the concentration of phosphate to be higher in the serum (see Table XIII) The concentration of calcium was lower in the fluid than in the serum, but the distribution ratios $\sqrt{\frac{Ca_f}{Ca_s}}$ were

reducing substances in the fluid were found to be fermentable by yeast The relatively high concentration of sugar in the fluid compared with that in the blood is difficult to explain

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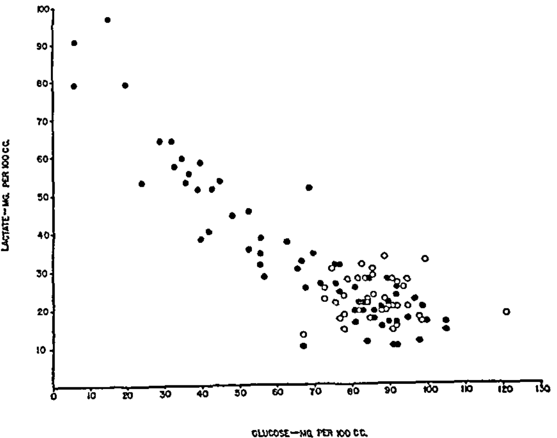



FIGURE 15 The relationship between the lactate and glucose concentrations in synovial fluids (•) and sera (o) in various joint diseases

somewhat higher than those found in normal human fluids, with only slight increases in the theoretical ratios (Table XIII) The relatively higher concentration of calcium and lower concentration of chloride and phosphate in pathological fluids are due presumably to the higher concentration of protein in these fluids Other electrolytes such as sodium and potassium have been determined only occasionally in pathological fluids In the few fluids that have been examined, the results have been such as would be expected from the findings in normal cattle fluid (See Table II and review of the subject[107]) The total base concentrations in 2 fluids from rheumatoid arthritis were 145 8 and 152 5 m eq /1 in contrast to 147 8 and 156 7 m eq /1 in the blood In the first of these cases, the sodium concentration in the fluid was 133 5 m eq /1 and that in the blood was 137 0 m eq /1

*Thiocyanate*

Diffusion of thiocyanate into the joint space is rapid It was detected in the synovial fluid of calves 10 minutes after intravenous injection[209] The concentration rose steadily until equilibrium was attained in from 1 to 5 hours At that point, the fluid level was 9 per cent lower than that of the blood The findings in 2 patients with a Charcot joint and in 3 of 7 patients with rheumatoid arthritis were similar In 3 of the rheumatoid patients, the rate of entrance was slower than that found in calves, while in 1 it was very rapid, equilibrium being attained in 15 minutes

*Hydrogen Ion Concentration*

The average pH of normal human fluid obtained post mortem is 7 39 as determined in this laboratory Widely varying values (ranging from 7 4 to 8 4) for normal fluid obtained post *mortem* or after amputation have been reported[149, 180, 208] In normal cattle fluid the average value is 7 31 in comparison with an average of 7 42 for the serum[187]

In joint disease, the pH varies with etiology and severity Determinations of pH were made on only 23 fluids in the present series In effusions from single cases of intermittent hydrarthrosis, gonococcal arthritis and mild rheumatoid arthritis, the pH of the fluid was approximately the same as that of the blood, being even slightly higher in 1 of these cases The pH of the fluid was defi-

| Type of fluid | Relative viscosity average at 38 C | Alkaline phosphatase average Bodansky units |
|---|---|---|
| Human knee | 235 (22) | 0 7 ( 5) |
| Cattle | | |
| carpometacarpal | 56 ( 4) | 8.2 ( 3) |
| astragalotibial | 3 ( 7) | 13 8 (16) |

The figures in parentheses indicate the number of fluids from which the averages were obtained

been considerable tissue destruction, as in severe cases of traumatic, infectious or rheumatoid arthritis Holmgren,[83] by means of X ray examination, demonstrated free fat in 26 of 41 cases of fracture of the knee

### ENZYMES

The enzymes of normal synovial fluid have not been studied in detail Podkaminsky[151] found an amylase, protease and lipase but no catalase We have found, however, that synovial fluid causes breakdown of hydrogen peroxide The alkaline phosphatase activity *in normal cattle fluid* is higher than that in the serum, an average of 13 8 units per 100 cc in contrast to 4 6 Variations in activity in the fluid are marked, with a range from 5 4 to 33 8 units per 100 cc In 5 fluids obtained post mortem from patients who had had no joint disease, the phosphatase activity was much lower than that in normal cattle fluid, ranging from 0 36 to 1 08 units per 100 cc In our experience, normal human fluid has the lowest phosphatase activity and the highest viscosity of any type of fluid This inverse relationship, apparent in the table above, may be of no significance but is interesting because serum with high alkaline phosphatase activity has been shown to cause breakdown of synovial mucin in vitro[165]

The phosphatase activity was relatively constant in the 9 fluids from various joint diseases studied in this series and was, in general, only slightly less than that of the serum, averaging 2 7 units per 100 cc in contrast to an average of 3 5 in the serum

It is apparent that knowledge of the various types of enzymatic activity in synovial fluid is too limited to indicate the role that enzymes play in the metabolism of articular structures

nitely lowered in more severe rheumatoid joints (8 cases), averaging 7 22 in comparison with 7 45 in the serum The greatest difference between fluid and blood in the rheumatoid cases was 0 36 In the only 2 fluids from cases of infectious arthritis (staphy lococcal and pneumococcal) that were examined, the pH values were 7 20 and 6 93 The serum pH in the latter case was 7 39

Following intravenous injection of weak electrolytes (sodium carbonate, lactic acid ammonium chloride and sodium salicylate), Joseph, Reed and Homburger[101] found that the pH of the joint (measured in vivo) changed more slowly than that of the blood The latter usually reached the maximal displacement in 1 minute (and approached the resting level within a few minutes), whereas the joint pH usually required more than 5 minutes for the maximal effect Femoral nerve stimulation or exercise of the joint produced *a decrease of the pH of both blood and joint fluid The blood pH* fell rapidly and returned within a few minutes to a normal level The fall in the joint pH came more slowly and the displacement was often maintained for 20 to 30 minutes Similar results were obtained when convulsions were produced with metrazol or insulin [19-] Following unilateral perivascular sympathectomy, the fall in joint pH following femoral nerve stimulation was greater on the operated side and in many cases showed no recovery in 30 minutes [160]

LIPIDS

Cholesterol and fatty acids are not found in normal cattle synovial fluid [169]

Cholesterol is present in the fluid in joint disease In 3 rheuma toid fluids, the distribution ratio between fluid and serum was 0 67, 0 58 and 0 82, it was 0 61 and 0 45 in 2 cases of arthritis of undetermined nature In the majority of instances the presence of cholesterol presumably indicates increased permeability of the tissues between blood and fluid and possibly a reduced rate of removal Chauffard Richet and Grigaut[34] and White and Sacks[207] found low levels of cholesterol in edema fluid due to congestive failure or venous obstruction in contrast to high con centrations in fluids originating from lymphatic obstruction However, in some cases the content of cholesterol is probably increased because of breakdown of tissue Free fat and cholesterol crystals are found often in fluids from joints in which there has

several years later, it became apparent that these patients had rheumatoid arthritis (see Case 6, p. 126).

In general, nonhemorrhagic traumatic fluids show relatively slight changes from normal. A typical fluid of less than 3 months duration is clear and does not clot. Total nucleated cell count in our 31 fluids usually was below 1,000 per cu. mm., with an absolute polymorphonuclear count below 100. The erythrocyte count varied from 50 to 15,650. The concentration of sugar was essentially the same as that of the serum. The protein content (exclusive of mucin) was 2 to 3 times that of normal fluid, most of the increase being in the albumin fraction, so that the albumin/globulin ratio remained high, with an average of 4.9. Electrophoretic patterns in 7 cases showed the albumin fraction always higher in the fluid than in the serum, alpha-1 and beta globulins essentially the same and alpha 2 and gamma-globulins lower in the fluid.[169] The viscosity was slightly reduced, but the mucin content per cubic centimeter was normal (0.076 gm. nitrogen and 0.098 gm. glucosamine per 100 cc.), and the mucin precipitated as a ropy clump in a clear solution.

Thus the findings in traumatic effusions of short duration indicate only slight inflammation. Effusions that persist for over 3 months following trauma may represent other types of arthritis, as discussed above. They showed somewhat more marked changes, with slightly higher cell counts and protein concentrations. The mucin concentration also was slightly increased, suggesting more rapid formation due to persistent irritation of synovial tissues.

While 40 traumatic effusions contained less than 20,000 erythrocytes per cu. mm. and were not xanthrochromic, 26 fluids were definitely hemorrhagic. In such cases, even when the fluid was aspirated within 16 hours, clots were not found and the bloody fluid usually did not clot after withdrawal. There is no evidence to indicate whether clotting occurs in the joint and the clots are dissolved or whether some constituent of the fluid acts as an anticoagulant. Volkmann[92] stated that absorption of blood takes place very slowly unless there is a tear in the synovial membrane and that blood often remains in fluid state in the joint for weeks or months. Julliard,[103] Kling[115] and Collins[39a] also noted that hemorrhagic traumatic effusions did not clot either in the joint

# III

## *Findings in Fluids in Group I, Diseases of Traumatic Origin*

THE characteristics of synovial fluid in the different forms of joint disease included in Group I and the number of fluids from which the data were obtained are shown in Figures 5, 6, 9, 10, 11, 12 and 14 and the chart at the end of the book.

### TRAUMATIC ARTHRITIS

Effusions frequently follow joint injuries of various types as would be expected. The effusions appear within a few hours after injury, usually subside within 1 or 2 weeks and seldom last more than 3 months. As a rule, the involved joints are not red, hot or acutely tender.

Persistence of symptoms and effusion for more than 3 months after injury suggests that the joint involvement, though precipitated by trauma, is not the result of trauma alone. However, it is frequently impossible to make any other diagnosis or to determine what additional factors are playing a role. Therefore, for this series we have included these cases (9 fluids) in a group designated "traumatic arthritis of over 3 months duration." It is possible that they all represent mild cases of other types of arthritis. For instance, infectious arthritis and gout tend to localize in traumatized joints, and trauma may precipitate the first marked joint involvement in rheumatoid arthritis. In such cases the joint disease often is incorrectly diagnosed. This is exemplified by 2 of the patients who were originally included in the group labeled "traumatic arthritis of long duration" and whose biopsies were interpreted as showing "chronic synovitis." On re-examination

represent examples of various other types of arthritis The microscopic changes were variable, as were the clinical histories of these cases, but in general they were consistent with a very mild degree of chronic inflammation The usual findings were slight villous hypertrophy, fixed cell proliferation and lympho cytic infiltration

Few studies on traumatic fluids have been reported by other workers Non hemorrhagic and hemorrhagic fluids have not in general been considered separately Rostock[173] found variations in intra articular pressure from 125 to 700 mm of fluid in 9 acute traumatic effusions associated with intra articular fractures In 35 hemorrhagic traumatic effusions not associated with intra articular fractures the pressures varied from 0 to 600 The range in chronic traumatic effusions was from 0 to 340 Ranke[158] reported pressures of 1 5 to 20 cm of mercury with an average of 9 cm in hemorrhagic effusions

The cytological findings of the present series are similar to those found by Julliard[103] (8 cases) and by Collins[39] (3 cases) but the total leukocyte and polymorphonuclear counts are in general lower than those of Shands[184] (4 cases), Kling[115] (88 cases), Keefer[104] (2 cases) McEwen[129] (2 cases) and Hirsch[85] (5 cases) The height of the total leukocyte and polymorpho nuclear counts which reached 12 000 per cu mm and 94 per cent in some of the fluids of the latter four series suggests that the joint effusions were not due to trauma alone

Reports vary concerning the relation between the pH of the synovial fluid and the duration of the effusion Lasch[120] in 10 cases found values varying from 7 39 in effusions of 2 days duration to 7 91 at the end of 1 year after injury On the other hand Beck and Lauber[15] noted pH values of 7 23 and 7 17 in 2 fluids taken 2 days and 3 weeks after injury values which changed to 6 80 and 6 86 respectively 2 days after the original aspirations Waugh[206] found an average pH of 5 65 in 20 traumatic effusions 24 hours after injury changing to 5 95 on the following day and reaching 7 7 on the seventh day Coppo and Levi[40] observed values of 7 67 and 7 94 in traumatic effusions but did not state the duration of the effusions

The chemical findings of Collins[39] in 5 traumatic effusions agree in most respects with those of the present series The amount of fluid varied from 12 to 40 cc the total protein including mucin from 3 25 to 3 35 per cent the sugar from 68 to 97 mg per 100 cc and the viscosity from 2 8 to 11 2 Kulonen[115b] in 9 fluids found viscosities ranging from 1 5 to 16 6 and in 2 fluids noted freezing points of 550 and 607 C In 1 fluid Ragan[155] found a viscosity of 13 8 In 27 fluids Sundblad[194] reported variations in the amount of fluid from 15 to 85 cc an average intrinsic viscosity of 41 0 an average total protein content of 4 42 gm per 100 cc and an average con centration of hyaluronic acid of 0 101 gm per 100 cc Kling[115] in 88 cases found an average icteric index of 14 with a range from 8 to 133 Pewny[150] stated that the protein concentration in traumatic fluids is 2 5 per cent

or after aspiration Davies,[43] however, stated that blood shed into normal or pathological joints clots very readily

Hemorrhagic traumatic effusions of under 3 months duration offered interesting comparison with non hemorrhagic traumatic fluids of similar duration The total nucleated cell and absolute polymorphonuclear counts were slightly higher in the 26 hemorrhagic fluids with averages of 1,540 and 315 per cu mm There were a marked increase in the erythrocyte count and, in many instances, a high icteric index The sugar concentration in the majority of the hemorrhagic effusions was decreased in contrast to other traumatic fluids, presumably because of the increased glucolytic enzyme content previously mentioned The average concentration of total protein was the same as that in the non hemorrhagic fluids The relative increase in globulin was greater than that of albumin as would be expected, so that the albumin/globulin ratio averaged 2 8 in contrast to 4 9 The viscosity varied markedly but covered essentially the same range as that of the non hemorrhagic fluids Although the mucin concentration varied, it averaged much less than that of the non hemorrhagic fluids (0 050 gm nitrogen and 0 019 gm glucosamine per 100 cc ), and the mucin precipitate with acetic acid was less cohesive

The relatively high concentration of protein and low concentration of mucin in hemorrhagic fluids are probably due to the fact that the effusion is formed partly by direct flow of blood into the joint Under such conditions less mucin is carried into the joint from the surrounding tissues Although the lower content of mucin might be due to destruction of mucin by an enzyme carried in with the blood this explanation is unlikely, since no such enzyme has been demonstrated in blood [170] Furthermore, the relationship of mucin concentration to viscosity in these fluids indicates that there is very little degradation of the mucin

It is apparent that hemorrhagic fluids resemble other traumatic fluids except for the changes directly related to the increased content of blood

Histological examinations of synovial tissue from traumatic arthritis were limited to lesions of more than 3 months duration and included 5 examples with non hemorrhagic and 2 with hemorrhagic effusions As stated above it is probable that effusions that persist for more than 3 months are not due to trauma alone but

of osteochondromatosis in this series were only slight The fluid was clear, did not clot and was extremely viscous Total nucleated cell count was only slightly above normal, averaging 507 per cu mm, average absolute polymorphonuclear count was only 5 The fluid sugar in the 1 case in which it was determined was 93 mg per 100 cc compared with 101 mg in the serum The average total albumin and globulin concentration was also only slightly above normal (2 2 gm per 100 cc ) and was a much lower value than that of traumatic fluids The extremely high mucin content, on the other hand, averaging 0 166 gm nitrogen and 0 99 gm glucosamine per 100 cc, was much greater than the average for normal human fluid and higher than that in any other type of joint disease (see p 56 for discussion) The viscosity was correspondingly high, with an average of 580 at 38° C The mucin precipitated with acetic acid as a ropy clump with clear surrounding solution

The findings in these cases indicate that there is only very slight inflammation in osteochondromatosis

Synovial tissues removed at biopsy in 5 cases showed slight evidence of inflammation with scanty lymphocytic infiltration The most characteristic changes were villous hypertrophy with many foci of cartilaginous metaplasia containing areas of calcification and cancellous bone formation There were also occasional small superficial patches of fibrin like material and foci of mucoid change of the connective tissue

### NEUROARTHROPATHY (CHARCOT JOINTS)

The marked degenerative changes, joint destruction and loss of pain sense that occur in Charcot joints afford an excellent basis for the development of traumatic effusions One or more joints may be involved and as a rule they are painless and not red, warm or tender Effusions usually are large and frequently persist for years

Of the fluids in this series, 31 were from Charcot joints associated with tabes dorsalis and 1 was secondary to syringomyelia There was no essential difference between the latter fluid and those from syphilitic patients Fluids from Charcot joints were very similar to traumatic fluids They were either clear or hemorrhagic and did not clot The intra articular pressure varied from

Scapini[118] in 1 case and Coppo and Levi[40] in 2 cases found calcium of 10 9 mg per 100 cc phosphorus of 2 4 and 3 1 mg per 100 cc magnesium of 2 7 mg per 100 cc, potassium of 29 mg per 100 cc chloride of 719 mg per 100 cc protein of 5 8 gm per 100 cc and a viscosity of 1 9 Schurch Viollier and Sullmann[127] reported that the albumin/globulin ratios in traumatic fluids were the same as those of the corresponding sera but the concentration of alpha 2 globulin was lower in the fluid than in the serum Olhagen[111] found the relative distribution of proteins in traumatic fluids about the same as in the plasma with slightly higher concentrations of albumin and gamma globulin in the fluid In hemorrhagic effusions resulting from moderate or severe injuries Efskind[51] found a delayed absorption of perabrodil and of indigo carmine from the joints

## OSTEOCHONDRITIS DISSECANS

Effusions occur frequently in osteochondritis dissecans Involvement is usually limited to one joint, most commonly the knee but may be bilateral, as in 1 case in this series The joints usually are not red, warm or tender

The 10 fluids in this series were essentially the same as traumatic fluids They were clear or slightly turbid and usually formed only a small clot on standing The average total nucleated cell count (750 per cu mm ) and percentage of polymorphonuclears (9) were in the same range as those of traumatic fluids The sugar concentration in the 2 fluids examined was 88 and 101 mg per 100 cc The average total albumin and globulin concentration (3 3 gm per 100 cc ) and the globulin fraction (0 8 gm per 100 cc ) were essentially the same as those of traumatic fluids The mucin nitrogen concentration in the 2 fluids examined was higher and the mucin glucosamine content in 1 fluid was lower than those of traumatic effusions The mucin precipitate was ropy with a clear solution The average relative viscosity was 23

The findings in fluids from osteochondritis dissecans indicate only slight inflammation

Synovial tissues in the 1 case examined, also showed only slight change from normal Scanty infiltration with lymphocytes and histiocytes was the principal abnormality

## *OSTEOCHONDROMATOSIS*

Effusions are not uncommon in osteochondromatosis Only one joint is involved and it is not red warm or tender

The abnormalities found in the synovial fluids from the 8 cases

Synovial tissues in 5 cases showed active fixed cell proliferation with marked hypertrophy of villi and fibrosis but relatively mild focal infiltration of lymphocytes Focal deposits of hemosiderin, fibrin like material, calcium and cartilaginous or bony metaplasia were common

Low nucleated cell counts and/or low percentages of polymorphonuclear cells were found also by Dufour[67] (1 case) Abadie[1] (3 cases) McEwen[124] (1 case) and Collins[39] (1 case), occasional higher counts were reported by Pewny[150] (17,000 cells per cu mm in 1 case) Shands[184] (up to 12 000 cells in 10 cases), Keefer[104] (18 350 cells in 1 of 3 cases) and Kling[115] (up to 260 000 cells in 6 cases) The explanation of such high counts is not ap parent

Few chemical studies have been made Keefer[104] found protein contents, including mucin ranging from 3 4 to 4 0 per cent in 3 cases Achard and Piettre[4] in 1 case have reported a mucin content of 41 8 gm , a fibrin content of 1 42 gm and a lipid level of 0 46 gm per 1 000 cc (It seems probable that the acetone precipitate of mucin contained proteins in addition to those combined with the polysaccharide ) Scapini[178] in 1 case and Coppo and Levi[40] in 3 cases found calcium concentrations ranging from 6 05 to 10 65 mg per 100 cc phosphorus from 2 5 to 2 9 mg per 100 cc magnesium from 1 5 to 2 7 mg per 100 cc , potassium from 13 8 to 28 9 mg per 100 cc chloride from 834 to 940 mg per 100 cc , pH from 7 65 to 8 14 protein from 4 1 to 4 4 gm per 100 cc and a viscosity of 1 65

Other workers have found that the Wassermann reaction in cases of Charcot joints is not consistently the same in serum and in fluid as shown in the table below In Poehlmann s[153] case the blood and fluid Wassermann reac tions were both positive but the fluid reaction was weaker

Wassermann Reaction in Serum and Fluid

| Investigator | Total no of cases | No of fluids in which serum and fluid differed | Result of Wassermann reaction | |
|---|---|---|---|---|
| | | | Serum | Fluid |
| Chesney[36] | 2 | 1 | Negative | Positive |
| Shands[184] | 4 | 2 | Positive | Negative |
| Keefer[104] | ?2 | 2 | Positive | Doubtful |
| Kling[115] | 6 | 1 | Positive | Negative |

## DEGENERATIVE JOINT DISEASE

The relative infrequency of effusions in degenerative joint disease is in accord with the pathological findings Apparently the initial and fundamental change occurs in the articular cartilage and consists of degenerative changes manifested by surface irregularities, swelling and fibrillation of matrix and abnormal cluster-

130 to 300 mm of fluid The total nucleated cell count in this series was normal (below 180 per cu mm ) in 7 of the 32 fluids and below 500 in 14 other fluids The percentage of polymorpho nuclears was normal in 16 out of 31 of the fluids Seventeen of the 32 fluids were grossly bloody or xanthrochromic, indicating that hemorrhage is common in neuroarthropathy, as described by Dufour,[57] Abadie,[1] Henderson,[84] Shands[184] and Kling[115]

The sugar concentration was essentially the same as that of other fluids of Group I, averaging 81 mg per 100 cc in com parison with an average of 92 mg per 100 cc in the serum The average lactate content in 2 fluids was 13 mg per 100 cc compared with 15 mg in the serum

*The average total albumin and globulin concentration was the* same as that of traumatic fluids, ranging from 1 8 to 5 1 gm per 100 cc, although the variations from case to case were much more marked Two of the highest protein concentrations were in 2 fluids from a patient who had areas of cellulitis near the joint affected, it can be assumed that the synovial tissue was involved in the inflammation The globulin concentration averaged slightly higher than in other Group I fluids, with an average albumin/globulin ratio of 2 2

The mucin concentration also varied similarly, but the average (0 068 gm nitrogen and 0 046 gm glucosamine per 100 cc) was below that of traumatic fluids The mucin precipitate with acetic acid was a ropy clump in clear solution in 15 cases, and less cohesive with slightly cloudy solution in the other 9 fluids examined Viscosity varied markedly, ranging from 2 7 to the exceptionally high value of 228, with an average of 31 at 38° C (see p 56 for discussion) The lowest viscosity (2 7) was that of a fluid obtained from the patient with areas of cellulitis near the joint

The Wassermann reaction in the fluid from Charcot joints was the same as that of the serum in 6 of the 8 cases in which both were tested (In 1 other case in which the reaction was positive in the fluid, the serum Wassermann was negative, but the Hinton was positive ) In 6 of the fluids, the reaction was negative

Thus the findings in Charcot joints are in general accord with *the fact that there is no marked inflammatory process in the* membrane

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## DEGENERATIVE JOINT DISEASE

The relative infrequency of effusions in degenerative joint disease is in accord with the pathological findings Apparently the initial and fundamental change occurs in the articular cartilage and consists of degenerative changes manifested by surface irregu- larities, swelling and fibrillation of matrix, and abnormal cluster-

ing of cartilage cells Subsequently there is increasing destruction of cartilage and overgrowth of bone at the capsular attachments As these changes proceed, the mechanics of the joint become poorer and even normal use may cause trauma with some degree of synovitis When effusions occur, they are rarely large and are often inconstant As a rule, they are produced by excessive use of the joints, though occasionally they are caused by acute trauma Involved joints are not red or hot, and although there may be some tenderness, this usually is not marked

Fluids from degenerative joint disease are essentially the same as traumatic fluids They are clear, very viscous and do not clot The average nucleated leukocyte count (720 per cu mm ) and the percentage of polymorphonuclears in the 18 fluids of this series were in the same range as in traumatic fluids The total concentration of albumin and globulin (2 6 gm per 100 cc ) and the albumin/globulin ratio (4 8) were also approximately the same as those of traumatic fluids The average concentration of mucin (0 095 gm nitrogen and 0 058 gm glucosamine per 100 cc ) was essentially the same as that of traumatic fluids It precipitated as a ropy clump in a clear solution except in 2 fluids in which the solution was slightly cloudy The relative viscosity (ranging from 13 to 78 at 38° C ) was somewhat higher than that of traumatic fluids This does not suggest that a loss of lubricating power is a factor in the production of the cartilage changes in this disease In fact, one of the highest viscosities of fluids examined in this laboratory was that of 1,285 in fluid obtained post mortem from a patient with marked degenerative changes but no effusion in the knees (the patient died at the age of 81, following perforation of the gall bladder) By teleological reasoning such an extremely high mucin content would suggest increased production of mucin in an attempt to provide better lubrication for damaged articular surfaces (See p 56 for a discussion of mechanisms which may produce high mucin concentrations )

Fluids from 11 cases of degenerative joint disease secondary to other joint abnormalities (such as congenital malformation of the hip) showed essentially the same changes as those from primary degenerative joint disease

The similarity of fluids from degenerative joint disease and those from traumatic arthritis is compatible with the hypothesis that synovitis associated with degenerative joint disease represents

reaction to the trauma resulting from the use of mechanically poor joints

Histological examination of the synovial tissues in 12 cases revealed slight diffuse and focal infiltration of lymphocytes, and occasional plasma cells and histiocytes In a few cases the infiltration was more marked Villous hypertrophy and diffuse fibrosis were present in varying degrees These changes were similar to those found in so called traumatic" effusions of over 3 months duration (p 78)

The earliest report of the characteristics of fluid in degenerative joint disease was that of Hoppe-Seyler in 1872[89] In 2 cases he found yellowish alkaline clear very viscous stringy fluid The mucin concentration was 2 3 per cent, the albumin 2 0 per cent, total solids 5 73 per cent Subsequent investigators[89, 104, 164, 194, 115, 163] have reported varied cytological findings Total leukocyte counts ranged from 200 to 11 000 per cu mm , with 0 to 88 per cent polymorphonuclears In the majority of cases the absolute polymorphonuclear count was in the range of the present series On the basis of our data total counts above 6 000 or absolute polymorphonuclear counts above 500 would suggest that other joint disease was superimposed on the degenerative disease Kling s report covers 46 cases of "osteoarthritis but includes cases with evidence of "acute inflammation some of which had high sedimentation rates Some of his figures therefore do not apply to uncomplicated degenerative joint disease

Studies of physical and chemical characteristics are meager The intra articular pressure in 2 cases studied by Rostock[172] was in the same range as that of various traumatic effusions (0 to 300 mm of fluid) There have been reports of values of pH from 7 3 to 7 8[115, 163] viscosities from 6 to 102[89, 115, 194] sugar from 95 to 100 mg per 100 cc[89] calcium from 8 1 to 14 mg per 100 cc[*, 115] uric acid from 2 7 to 5 9 mg per 100 cc[115] icteric index from 2 1 to 4 6[115] protein contents from 3 3 to 3 7 per 100 cc[163, 194] and hyaluronic acid of 0 146 gm per 100 cc[194] A relative viscosity of 6 suggests that other joint disease was superimposed on the degenerative joint disease

*A calcium content above that of the serum is very unusual and has been found in our series only in 3 patients who had rheumatoid arthritis and vitamin D poisoning and in 2 patients who had diseases that could not be definitely diagnosed but fell in the group of generalized connective tissue diseases In all these cases the fluid was milky or pasty and on analysis contained high concentrations of calcium (from 12 4 to 35 9 mg per 100 cc ) and phosphorus (from 9 2 to 18 4 mg per 100 cc ) with calcium/phosphorus ratios of approximately 2 0 In the 3 cases of vitamin D poisoning there was in addition a white granular sediment in which the ratio of calcium to phosphorus was much higher (approximately 4 7) and entirely unlike that of bone In material from an inflamed subacromial bursa the calcium concentration was 13 9 mg per 100 cc but the equilibrium between bursa and serum differs from that between joint and serum (see discussion of bursae p 120)

ing of cartilage cells. Subsequently there is increasing destruction of cartilage and overgrowth of bone at the capsular attachments. As these changes proceed, the mechanics of the joint become poorer and even normal use may cause trauma with some degree of synovitis. When effusions occur, they are rarely large and are often inconstant. As a rule, they are produced by excessive use of the joints, though occasionally they are caused by acute trauma. Involved joints are not red or hot, and although there may be some tenderness, this usually is not marked.

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SUMMARY OF FINDINGS IN GROUP I FLUIDS

It is apparent that the fluids in Group I show relatively slight changes from normal In general, the amount of fluid is increased but the unit concentration of nucleated leukocytes and the absolute number of polymorphonuclears are only slightly above normal The total concentration of albumin and globulin is increased but remains below 5 gm per 100 cc, and the albumin/globulin ratio remains above 1 40 The concentrations of sugar and of mucin, except in osteochondromatosis, tend to be normal or only slightly lowered The viscosity is somewhat reduced except in osteochondromatosis, but mucin precipitates normally

# IV

## *Findings in Fluids Resembling Both Groups in Some Respects*

THE changes in fluids obtained in cases of hypertrophic pulmonary osteoarthropathy, hemophilia, disseminated lupus erythematosus, gout, rheumatic fever, arthritis due to hypersensitivity, erythema nodosum, hemorrhagic villous synovitis and tumors are more marked than those of Group I fluids, as will be shown In general, however, these fluids are not so abnormal as those of Group II (Figures 5, 6, 9, 10, 11, 12, 14, and chart at back of book )

### HYPERTROPHIC PULMONARY OSTEOARTHROPATHY

The synovial tissues are occasionally involved in hypertrophic pulmonary osteoarthropathy Effusions may occur and persist for the duration of the disease The joints are painful, but usually not red, hot or tender

Most of the findings in fluids from hypertrophic pulmonary osteoarthropathy are similar to those in traumatic fluids The fluids are clear and viscous, but, in contrast to traumatic fluids, they usually clot The intra articular pressure in this series varied from 0 to 150 mm of fluid The average nucleated leukocyte count in the 6 fluids was only slightly higher than that of traumatic fluids (1,830 per cu mm ), and the percentage of polymorphonuclears remained low (15 per cent) The sugar content was essentially the same as that of the serum The total concentration of albumin and globulin was in the same range as that of traumatic fluids, although the albumin/globulin ratio was lower in the fluids from cases of osteoarthropathy (2 1) The mucin concentration also tended to be lower than in traumatic fluids with a

lower viscosity (15) The mucin precipitate was ropy in 1 case but soft in 2 other fluids, solutions were relatively clear

Summation of the findings in these fluids indicates slightly greater inflammation than in the traumatic joints

Histological examination of synovial tissues from 2 cases disclosed slight to minimal infiltration of lymphocytes, plasma cells and histiocytes, some hyperplasia of synovial cells, and fibrosis

HEMOPHILIC ARTHRITIS

The joint effusions of patients with hemophilia result from bleeding into the articular space They are reabsorbed slowly and, when repeated hemorrhages occur, often persist for weeks or months At the onset, the joints are usually markedly swollen, painful, warm and tender

The fluids are grossly bloody but do not clot The total leukocyte counts of the 5 fluids of this series averaged 5,320 per cu mm, with an average of 38 per cent polymorphonuclears The concentration of sugar was slightly below normal The average total albumin and globulin concentration was relatively high, 5 94 gm per 100 cc, but the average globulin was only 1 8 gm, with a resulting albumin/globulin ratio of 2 4 The average relative viscosity was 21 at 38° C The average mucin content (0 041 gm nitrogen per 100 cc) was slightly lower than the average for hemorrhagic traumatic fluids The mucin precipitate was ropy in 1 case but formed only shreds in 2 other fluids

The findings in hemophilic fluids indicate somewhat more marked inflammation than is reflected in the majority of Group I fluids The reaction is comparable to that found by Key[103a] after repeated intra articular injections of blood into rabbits joints

SCURVY

Joint effusions in scurvy occur presumably as a result of bleeding into the joint

The 1 fluid in this series from a patient with scurvy was bloody and did not clot The total leukocyte count was 300 per cu mm with 4 per cent polymorphonuclears The erythrocyte count was 1,040,000 The sugar content was 75 mg per 100 cc compared with 83 mg in the serum The mucin precipitate was soft in a clear solution, and the viscosity was 9 6

Scapini[10] in 1 case of scurvy found a chloride content of 869 mg per 100 cc., phosphorus of 2 8 mg per 100 cc, calcium of 11 9 mg per 100 cc, potassium of 29 4 mg per 100 cc and magnesium of 3 1 mg per 100 cc Coppo and Levi[6] in 1 case reported a protein content of 2 1 gm per 100 cc and a pH of 8 23

LUPUS ERYTHEMATOSUS DISSEMINATUS

Joint effusions occur in lupus erythematosus disseminatus but are relatively uncommon and often of small size Only occasionally are the joints red, hot or acutely tender

The fluids may be clear or turbid, are usually very viscous and do not clot The average nucleated leukocyte count in the 21 fluids of this series was higher than that of traumatic fluids (2,860 per cu mm ), but the polymorphonuclears remained very low (5 per cent) in lupus effusions * It is interesting that other body fluids (pericardial, pleural) from patients with this disease also show very low absolute polymorphonuclear counts, in fact, they often contain no polymorphonuclears Similarly, there is usually a leukopenia and an abnormally low percentage of polymorphonuclears in the blood The average concentration of sugar was 75 mg per 100 cc, with an average serum sugar of 97 mg per 100 cc The average total albumin and globulin concentration was even lower than that of traumatic fluids, but the globulin concentration was somewhat higher, resulting in a relatively low albumin/globulin ratio (1 3) The concentration of mucin nitrogen, on the other hand, averaged higher than that of traumatic fluids, with a high average viscosity of 149 at 38° C The mucin glucosamine concentration, 0 059 gm per 100 cc, however, was lower than that of traumatic fluids The mucin precipitated well in a firm, ropy clump with a clear solution

These fluids resemble traumatic fluids in most respects, but the slightly higher leukocyte count and the higher globulin are indicative of more severe inflammation The absence of polymorphonuclear response and the high concentration of undegraded mucin are characteristic

Histological examination of the synovial tissues in 6 cases showed minimal to moderate chronic synovitis with superficial fixed cell proliferation and infiltration of lymphocytes plasma cells and

*So called 'L E cells have been found (in concentrations of 2 and 3 per cent) in only 2 fluids from 1 patient

larger mononuclear cells There were also occasional thin superficial patches of fibrin like material In 2 cases there was necrotizing inflammation of small blood vessels with frequent fibrin thrombi, fragmentation of neutrophils and occasional hematoxylin bodies One of these lesions also showed some increase in faintly staining hematoxylinophilic ground substance

## GOUT

Reaction to the deposition of urates in articular tissues is presumed to explain the frequent occurrence of effusions in gout Such effusions are often very large, but usually subside within a few days Several joints may be involved at the same time In the acute attack, the joints are red, hot and acutely tender The swelling is marked, extending well beyond the limits of the joints

The changes in fluids from gout are somewhat greater than those in typical fluids of Group I and resemble Group II fluids in many respects The fluids are turbid and not very viscous and usually form fairly large clots The intra articular pressure in this series varied from 0 to 420 mm of fluid The total leukocyte count and the percentage of polymorphonuclears in the 24 fluids were considerably higher than those of traumatic fluids, averaging 13,317 per cu mm and 71 per cent respectively Concentrations of sugar and of uric acid however, were essentially the same in serum and fluid In 1 of 20 fluids the sugar concentration was very low (15 mg per 100 cc ) The lactate content in this fluid was 97 mg per 100 cc compared with 22 mg in the serum In 3 other fluids the average concentration was 31 mg per 100 cc with 29 mg in the serum The total albumin and globulin concentration was approximately the same as that of traumatic fluids and somewhat lower than the average for fluids of Group II The globulin fraction was relatively low, with a resulting average albumin/globulin ratio of 1 8 The average viscosity was 17 at 38° C The average mucin concentration was lower than that of normal or traumatic fluids The mucin precipitated usually very poorly in shreds with cloudy solution, though in 7 fluids the precipitate was ropy and the solution clear

The findings in gout indicate moderately severe inflammatory changes

Histological examination of synovial tissues discloses an inflam-

matory, proliferative reaction As described by Bennett,[16a] the articular tissues are progressively destroyed by the increasing amounts of urates that are deposited and by the chronic inflammatory and foreign body reaction that accompanies their deposition

Kling[113] has reported on synovial fluid from 4 cases of gout The white count varied from 1 600 to 13 600 per cu mm with polymorphonuclears from 65 to 78 per cent Burman[36] found uric acid concentrations of 6 3 and 6 2 mg per 100 cc corresponding to 6 7 and 5 6 mg in the blood The uric acid in Kling s fluids varied from 4 1 to 8 5 mg per 100 cc Our results do not support his finding that the concentration of uric acid in the fluid is significantly higher than that of the blood during an acute attack of gout (see table p 65) Such an elevation of the concentration of a diffusible substance in the fluid would not be expected in view of the evidence indicating ready diffusion in both directions between blood and fluid

## RHEUMATIC FEVER

Effusions in rheumatic fever occur usually in one or a few joints at any one time and ordinarily last only a few days The joints are moderately swollen and may be very tender, red and hot The findings in the fluids vary markedly, but, in general, are more like those in Group I than in Group II

The fluids are usually viscous and only slightly turbid Many of them clot, especially if the effusion is of only 1 or 2 days duration The intra articular pressure in this series ranged from 0 to 150 mm of fluid The total nucleated leukocyte count in the 20 fluids varied from 300 to 98,200 per cu mm , averaging 17,820 and the percentage of polymorphonuclears from 2 to 98, with an average of 50 Both tended to be higher in effusions of short duration (1 to 2 days) Polymorphonuclear cells usually predominated during the first 2 or 3 days of the effusion but were then replaced by monocytes and clasmatocytes and eventually by lymphocytes (see Table III) The concentration of sugar was essentially normal, averaging only slightly lower than that of the serum The lactate content of 1 fluid was 15 mg per 100 cc compared with 20 mg in the serum The average total albumin and globulin concentration was 3 74 gm per 100 cc , approximately the same as that of Group I fluids The albumin/globulin ratio remained high with an average of 3 1 The mucin concentration (0 108 gm nitrogen and 0 093 gm glucosamine per 100 cc ) was approximately the same as that of normal and traumatic fluids

and higher than that of Group II fluids The average viscosity (22 at 38° C ) was correspondingly higher than that in Group II In 10 of 13 cases the precipitate with acetic acid was ropy and the surrounding solution clear, in contrast to the precipitate obtained from rheumatoid effusions, which in most cases broke up into small pieces or appeared merely as a cloudy solution

Although these findings resemble, in general, those found in mild cases of rheumatoid arthritis (see p 112), the changes are more like those in the fluids of Group I than those in Group II

Histological examination of the synovial tissues, as described by Collins,[39a] reveals at the height of the acute inflammation, marked edema and dilatation and engorgement of blood vessels In this acute stage, moderate infiltration with lymphocytes and neutrophil polymorphs is found, especially toward the surface Later, polymorphs tend to disappear, as in the synovial fluid, lymphocytic invasion is more notable, and focal areas of fibrinoid degeneration with moderate proliferation of histiocytes and fibroblasts are found

McEwen[128] in a study of 40 rheumatic fever fluids found similar variations with total nucleated cell counts of 800 to 47,600 per cu mm and percentage of polymorphonuclears from 2 to 98 He noted a tendency toward higher counts in the first 7 days of effusion and an increasing number of polymorphonuclears when the arthritis was increasing in severity especially in patients under 20 years of age A gradual replacement of polymorphonuclears by monocytes and clasmatocytes and eventually by lymphocytes comparable to that in the present series was noted by McEwen[128] and Labor and von Balogh[11] Keefer Myers and Holmes[104] Collins[39, 39a] and Labor and von Balogh[119] found total counts varying from 1 000 to 50 000 with polymorphonuclears from 83 to 97 per cent Achard and Loeper[1] reported 4 cases in which the cells were again almost exclusively polymorphonuclears Keefer Myers and Holmes[96] reported total protein concentrations (including mucin) of 2 0 and 4 7 per cent Beck and Lauber[15] found a pH of 6 86 in 1 case while Boots and Cullen[23] in 16 fluids found variations from 7 27 to 7 42

### ARTHRITIS DUE TO HYPERSENSITIVITY

In sensitivity reactions joint involvement may occur, varying from arthralgia to moderately severe arthritis The joints are swollen red, tender and warm and usually subside within a few days

The 1 fluid in this series obtained from a patient with a severe reaction occurring 10 days after injection of penicillin, was clear

and did not clot The total leukocyte count was 450 per cu mm, with 28 per cent polymorphonuclears The mucin precipitated in a large, tight clump, leaving a clear solution The relative viscosity was extremely high 253 at 38° C

In joint effusions associated with serum sickness Boots and Swift[11] found total leukocyte counts from 4 160 to 22 400 per cu mm, with 13 to 86 per cent polymorphonuclears They noted a decrease in total leukocyte and polymorphonuclear counts with increased duration of effusion

### ERYTHEMA NODOSUM

Joint involvement in association with erythema nodosum is common, varying from arthralgia to moderately severe arthritis The joints may be swollen, red, painful and tender

The 1 fluid in this series from a patient with erythema nodosum was cloudy, yellow and clotted The total leukocyte count was 1,275 per cu mm with 16 per cent polymorphonuclears The content of sugar was the same as that of the serum The mucin precipitated with acetic acid as a fairly tight clump with clear surrounding solution

### HEMORRHAGIC VILLOUS SYNOVITIS

Effusions occur commonly in so called hemorrhagic villous synovitis or pigmented villo nodular synovitis, often in association with hemorrhage Involvement is usually limited to one joint which is only slightly tender and not red or hot The swelling often persists for years, though occasionally it recurs intermittently and disappears in a few weeks The findings in the fluids resemble those in Group II somewhat more than those in Group I

The fluids are usually bloody and not very viscous and usually do not clot The total nucleated cell count in 15 fluids averaged 3,110 per cu mm, with an average of 26 per cent polymorphonuclears The erythrocyte count varied from 43 400 to 1,780,000 The average concentration of sugar in the fluid was 73 mg per 100 cc as compared with 94 mg in the serum The average total albumin and globulin concentration was slightly higher than that of traumatic fluids, 4 23 gm per 100 cc The concentration of mucin, on the other hand, was low, with an average of 0 032 gm nitrogen and 0 049 gm glucosamine per 100 cc and a low average viscosity of 5 4 at 38° C The mucin precipitate was soft, often in

shreds, with a cloudy solution in 10 of the cases, but ropy with clear solution in the other 5 fluids

Thus the findings in fluids from hemorrhagic villous synovitis indicate only a mild to moderate degree of inflammation

Synovial biopsies from 4 cases showed mild to moderate infiltration of lymphocytes and plasma cells, as well as the characteristic hypertrophic matted villi, multiple hemorrhages, and numerous large, hemosiderin laden, rounded, polygonal or spindle shaped macrophages There were also widespread fixed cell proliferation, fibrosis with hyalinization, and occasional superficial patches of fibrin-like material In 3 lesions there was in addition a granulomatous reaction with multinucleated giant cells, foam cells and, in 1 instance, large free fat globules Opinion varies as to whether this lesion represents an inflammatory process or a neoplasm such as a benign giant cell tumor or a sclerosing hemangioma

Jaffe[96] noted that the synovial fluid from cases of pigmented villo nodular synovitis was often hemorrhagic

NEOPLASMS

Tumors involving joints may be benign or malignant, primary or metastatic In all cases, effusions may occur but usually are not large The tumors in this series may be divided into two groups one including 1 osteogenic sarcoma associated with Paget s disease, 1 synovioma 1 myxofibrosarcoma, and 1 metastatic papillary adenocarcinoma, and the other including 2 cases of lymphoma, Hodgkin s type, and 2 cases of lymphocytic leukemia

The fluids in both groups presented abnormalities greater, in general, than those of Group I the changes being more marked in the lymphoma group The 4 sarcoma and carcinoma fluids were hemorrhagic and formed small clots Their average total nucleated cell count (1,330 per cu mm ) and the percentage of polymorphonuclears (9) were in the same range as those of traumatic fluids Their average total albumin and globulin concentration (4 3 gm per 100 cc ), mucin nitrogen content (0 030 gm per 100 cc ) and viscosity (18 at 38° C ) were slightly more abnormal than those of Group I In the lymphoma group, the average total nucleated cell count (11 190 per cu mm ) and percentage of poly-

morphonuclears (27) were higher than in Group I The average total albumin and globulin content and the concentration of mucin in 2 fluids were in the same range as in Group I fluids, but in the 1 fluid analyzed the concentration of globulin was higher and the viscosity lower than in Group I fluids

Thus the findings in fluids from joints containing tumors indicated only moderate inflammation

Histologically, the synovial tissues from the 3 patients with myxofibrosarcoma, synovioma and adenocarcinoma showed minimal inflammation with slight villous hypertrophy In the 2 latter cases there was an increase in mucinous ground substance

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tissue and only a slight or moderate increase in the amount of fluid in the joint. The synovial fluid in such cases, though negative on culture, does reflect the tissue inflammation, but the leukocyte count usually is not more than 30000 per cu. mm., concentration of sugar is only slightly decreased and mucin is only partially broken down. The percentage of polymorphonuclears, however is usually very high averaging 92% suggesting the presence of infection. It is often difficult to prove that these cases are infectious in nature, but the above-mentioned experimental evidence and the synovial fluid findings indicate that the best explanation of such arthritides is the entrance of bacteria, not just "toxins," into the synovial tissues The following report is representative of such cases.

A [illegible]-year-old woman had developed empyema after removal of the lower lobe of the left lung because of bronchiectasis. Following rib resection and insertion of a tube, she had remained free of symptoms for 1 month. Three days before admission, drainage from the tube ceased and the patient developed fever chills, malaise and increased cough with foul sputum Three days later both knees became very painful and swollen. At the time of admission, the knees were red and tender and contained effusions the left ankle, both elbows and first metacarpophalangeal joint on the left were painful and swollen. Temperature was 102.4° F Synovial fluid from the left knee contained 20 000 leukocytes per cu. mm., of which 98 per cent were polymorphonuclears. The relative viscosity of the fluid was 10 6 at 38 C. the sugar (93 mg. per 100 cc.) was equal to that of the serum the protein content was 4.9 gm. per 100 cc. with a globulin concentration of 2.8 gm and the mucin (0 08 gm. nitrogen per 100 cc.) precipitated in a soft clump with cloudy filtrate Cultures from the sputum showed *B hemolytic streptococci* but cultures of the fluid from the left knee were negative The redness and swelling of the knees subsided fairly rapidly and 2 days after the first aspiration only 1 cc. of fluid could be obtained from the left knee The leukocyte count in this fluid was 17 500 per cu mm with only 75 per cent polymorphonuclears and 15 per cent lymphocytes

In one case we were able to watch the progression of the arthritis from early involvement with negative culture in the fluid to a more advanced stage in which organisms could be grown from the fluid

The patient, a woman of 63 was admitted with a complaint of pain in the right ear for 10 days with drainage of pus for 6 days She was known to have had severe diabetes for 9 years and relatively mild rheumatoid arthritis in hands wrists and ankles for 30 or 40 years A simple mastoid

# V

## Findings in Fluids in Group II, Rheumatoid Arthritis and Diseases of Infectious Origin

### SPECIFIC INFECTIOUS ARTHRITIDES

EXPERIMENTAL work in animals has shown that the barrier between the blood and the joint cavity is permeable, not only to diffusible substances and proteins, but to bacteria (see review[17]) and that the permeability of synovial tissues is greater than that of the membranes of other body cavities. Studies of synovial *fluids and synovial tissues obtained post mortem from patients* who died with generalized infection[37] have demonstrated that the tissue may show an inflammatory reaction which is reflected in the cytology of the fluid even though histological sections and cultures fail to show bacteria in either tissues or fluids (see p. 22).

The reaction of joints to infection varies markedly. The differences in the degree of joint involvement in generalized infections are apparent clinically and may range from mere arthralgia to arthritis of varying degrees of severity. Such differences are seen with all types of infecting agents and are well exemplified in gonococcal arthritis. There may be no effusion, a moderate sized sterile effusion or a large purulent effusion with positive culture. The explanation of the variations would seem to be that in all cases of infectious arthritis the organisms reach the synovial tissues but that the reaction depends on the extent to which the organisms can continue to multiply. This is determined by the number, type and virulence of the organisms and the local and general resistance of the patient. When multiplication of the organisms is limited and the reaction remains confined to a small area in the synovial tissues there is little or no destruction of

counts in 30 fluids averaged 73,370 per cu mm —higher than in any other type of fluid—with 90 per cent polymorphonuclears Some fluids consisted of thick pus, with too many cells to count The average total concentration of albumin and globulin in the fluids was high (4 79 gm per 100 cc ), with a relatively low albumin/globulin ratio (1 7) in accord with the severe degree of inflammation The unit concentration of mucin nitrogen was lower than normal and essentially the same as in other Group II fluids The relative viscosity varied from 2 9 to 37, averaging 16 at 38° C In fluid withdrawn within a few hours after the onset of arthritis, the mucin precipitate was often relatively normal In effusions of longer duration, it formed a soft mass or was flocculent In occasional severe cases, no mucin was precipitable with acetic acid The pH values in 2 cases were 6 93 and 7 20 The average concentration of sugar (21 mg per 100 cc ) was lower in the fluids from septic arthritis than in any other type, even though the average fasting concentration in the blood was elevated (112 mg per 100 cc )

The hyperglycemia found in the patients with infectious arthritis is of interest An increase in the fasting blood glucose level (above 100 mg per 100 cc ) was found in 16 of 20 samples from 11 cases of septic" arthritis and in 30 per cent of the cases of gonococcal arthritis It was apparently related to the severity of the infection having been found in 3 of 5 cases of gonococcal arthritis with positive fluid cultures (see p 102) It was most extreme in the case of pneumococcal arthritis (186 mg per 100 cc )

It is apparent that the fluid findings in septic arthritis indicate a severe inflammatory process with resulting high total leukocyte and polymorphonuclear counts low viscosity lowered sugar con centration high protein content and a poor mucin precipitate

Histologically, the synovial tissues from 4 cases of infectious arthritis (including gonococcal) varied from a suppurative necrotizing reaction with superficial destruction of the synovialis and a heavy fibrino-purulent exudate, to a subacute inflammation with marked hyperplasia of fixed cells and diffuse infiltration of plasma cells and lymphocytes as well as neutrophils and eosinophils

Other workers have found similarly high total cell counts and percentage of polymorphonuclears with variations from 2 400 to too many cells to

ectomy was performed and a few fresh granulations were found on the lateral sinus Ten days after operation she began to run a septic type of fever to 103 F and developed pain and swelling in the right knee and her blood culture showed Type 23 *Pneumococcus* Ten days later the right elbow became painful and swollen Sulfapyridine treatment (6 gm a day) was started and fever subsided slowly Symptoms in the right knee persisted and examination showed marked tenderness thickening of the periarticular tissues and pain on motion although the range of motion was essentially normal Two weeks later the swelling and tenderness in the knee were subsiding slowly but the patient had sudden onset of dyspnea and tachy cardia developed peripheral shock and died

When pain and swelling first appeared in the knee, it was thought that they were manifestations of an exacerbation of rheumatoid arthritis even though she had had no involvement of knees previously The culture of fluid withdrawn at that time was negative and the total leukocyte count was 10,650 cells per cu mm However, the high percentage of polymorphonuclears (96) and the marked tenderness of the periarticular tissues sug gested that pneumococci were present in the synovial tissues even though they could not be cultured from the fluid Culture of fluid withdrawn 7 days later showed rare colonies of Type 23 *Pneumo coccus*, and the total leukocyte count was 25,600 per cu mm with 98 per cent polymorphonuclears

The synovial fluid findings in arthritides due to various organ isms will be presented under separate headings

*Septic Arthritis (Due to Streptococci, Staphylococci, Pneumococci and E coli)**

Joint infections caused by streptococci staphylococci, pneumo cocci and *E coli* usually progress to so called septic arthritis with grossly purulent fluids and positive fluid cultures The effu sions are usually large and of short duration The joints are red hot and acutely tender, with the swelling often extending well beyond the limits of the joints The arthritis subsides, with varying degrees of joint damage, or the disease terminates fatally in a relatively short time

The synovial fluid is very turbid and not very viscous and forms a large, firm clot soon after withdrawal The total nucleated cell

*Gonococcal and meningococcal arthritis although they are also types of septic" arthritis will be discussed separately

(0 064 gm nitrogen) Viscosity was low (4 at 38° C ) in the 1 fluid with positive culture examined, and ranged from 3 to 21 with an average of 13 in the sterile fluids

Further evidence of simultaneous variation in fluid findings and in the severity of the joint disease was provided by cases of gonococcal arthritis in which the joints were aspirated before and during sulfanilamide treatment The signs of decreasing severity were a smaller volume of fluid and a reduction in total nucleated and absolute polymorphonuclear counts (see Table III)

Gonococcal complement fixation was positive in 18 (72 per cent) of the 25 fluids in which it was tested In 21 of the 25 it was the same as that of the serum In 2 cases it was negative with a positive reaction in the serum, in 1 it was negative with a doubtful reaction in the serum and in 1 it was positive with a negative reaction in the serum It may be concluded that the reaction in the fluid, being essentially a reflection of that of the blood, does not really aid in diagnosis

To summarize The findings in fluids from gonococcal arthritis show the marked variations which would be expected from the clinical differences found between individual cases of this disease In general, the fluids resemble those from other types of specific infectious arthritis but positive cultures are less common, as fewer effusions become septic" The fluids from which organisms can be cultivated show characteristic differences in cells, sugar and globulin from those of sterile fluids A positive culture is expected when a fluid contains more than 30 000 leukocytes per cu mm and less than 50 mg of sugar per 100 cc

Results of studies by other workers also show marked variations in fluids from gonococcal arthritis Total nucleated cells and polymorphonuclears varied from 1 000 to 158 000 per cu mm and from 22 to 100 per cent respectively in the cases of Labor and von Balogh [118] 1 case of Risak and Winkler [163] 1 case of Forkner [74] 1 case of Shands [164] 3 fluids of McEwen [128] 77 fluids of Myers Keefer and Holmes [137] 5 fluids of Collins [39] and 21 fluids of Kling [115] Julliard [108] and Kling [115] noted reduction in the percentage of polymorphonuclears and increase in lymphocytes and monocytes in subacute and chronic cases

The physical and chemical findings reported in the literature are relatively meager but also show marked variation from case to case Habler [81] reported a pH of 6 93 compared with a blood pH of 7 33 in 1 case with negative culture and Coppo and Levi [40] found a pH of 7 75 in 1 case There have

count and from 73 to 100 per cent polymorphonuclears[86, 104, 115, 128] The pH has been found to be more acid than in other types of fluids (except the traumatic effusions of 24 hours duration reported by Waugh[206]), being 6 19 and 6 69 in Boots and Cullen s[23] 2 cases, 5 60 in Beck s and Lauber s[15] case and 6 56 and 7 24 in Habler s[81] 2 cases The viscosity varied from 6 to 16 in Kling s[115] 2 cases Rostock[173] found intra articular pressures from 150 to 420 mm of fluid and Ranke[148] from 2 0 to 5 5 cm of Hg Sugar varied from 19 to 43 mg per 100 cc in 4 cases reported by Allison Fremont Smith Dailey and Kennard[7] In 15 cases Sundblad[194] found an average protein concentration of 5 30 gm per 100 cc and average hyaluronic acid content of 0 153 gm per 100 cc

*Gonococcal Arthritis*

In gonococcal arthritis, effusions may occur in one or in many joints The severity of involvement varies markedly, with the result that the joint findings may range from redness, heat and tenderness to only slight warmth and tenderness The effusions usually last only a few days but may persist for weeks The residual joint damage varies with the severity and duration of the arthritis

The fluids in this series showed the same general changes as other Group II fluids, but there was a wide range of variation in accord with the varying degrees of severity The findings in the 9 fluids from which gonococci were cultured differed from those in the 33 sterile fluids and closely resembled the findings in other septic synovial effusions (see Table IV) The fluids with positive cultures tended to be more turbid and almost always clotted The leukocyte count was usually above 30,000 per cu mm in these, and below 30,000 in the sterile, fluids The average concentration of sugar in the sterile fluids was only slightly below normal (83 mg per 100 cc, with an average serum level of 100 mg), but the average in the fluids from which gonococci were cultured (29 mg per 100 cc, with an average serum level of 113 mg—see p 101) was as low as that of other septic fluids The average lactate content in 4 sterile fluids was 39 mg per 100 cc compared with 20 mg in the serum The average total albumin and globulin content was essentially the same in both types of fluid (5 3 and 5 6 gm per 100 cc), but the average albumin/globulin ratio was definitely higher in the sterile fluids (1 7 as compared with 1 4) The mucin nitrogen concentration was lower in the fluids with positive cultures (0 041 gm nitrogen per 100 cc) than in the sterile fluids

The average total albumin and globulin (4 3 gm per 100 cc ) was slightly lower than that of other types of infectious arthritis, but the globulin fraction was relatively high (2 4 gm ), with an albumin/globulin ratio of 0 9 The average concentration of mucin (0 058 gm nitrogen and 0 027 gm glucosamine per 100 cc ) and viscosity of 15 at 38° C were similar to those of other Group II fluids The mucin precipitate was fairly cohesive with clear solution in 10 of the 18 fluids examined, but in shreds with cloudy solution in the other 8 fluids

In summary, the findings in fluids from meningococcal arthritis resemble those in gonococcal arthritis The incidence of positive cultures is much lower and the reduction in sugar concentration is less marked in meningococcal fluids, but the leukocyte count tends to be higher

Cattell[55] reported from 39 400 to 78 700 leukocytes per cu mm with 98 to 100 per cent polymorphonuclears in 1 case of meningococcal arthritis The concentration of sugar in 1 fluid was too low to read when the serum sugar was 81 mg per 100 cc The protein concentration in the fluid was 4 7 gm per 100 cc compared with 4 86 gm in the serum

*Haverhill Fever*

The arthritis of Haverhill fever, due to the *Streptobacillus moniliformis* is similar to other types of infectious arthritis The degree of involvement varies from arthralgia to severe purulent arthritis Residual damage varies in accordance with the severity of the involvement The 1 fluid of this type in our series was turbid and had a total leukocyte count of 42,000 per cu mm , with 87 per cent polymorphonuclears The sugar concentration was 80 mg per 100 cc

*Arthritis Associated with Bacillary Dysentery*

Involvement of joints occasionally occurs in association with bacillary dysentery The arthritis resembles other types of infectious arthritis varying in severity The effusions may last several months Severe residual damage is rare

The 1 fluid of this kind in our series was turbid and did not clot Organisms were not cultured from the fluid The agglutination titer for Hiss Y strain was 1/180 as compared with 1/320 in the blood The total leukocyte count was 7 500 per cu mm , with 79 per cent polymorphonuclears The concentration of sugar was

been reports of viscosities varying from 4 1 to 16 8[80,116,136] sugar contents (not all in fasting patients) from 38 to 131 mg per 100 cc[80,137] and total protein contents (including mucin) from 3 6 to 8 5 per cent[116,137] Achard and Piettre[4] reported mucin concentrations from 38 5 to 49 0 gm per 1 000 cc (It is probable that the acetone precipitate of mucin contained proteins other than those combined with the polysaccharide ) Scapini[176] in 1 case found a calcium content of 12 7 mg per 100 cc phosphorus of 5 6 mg per 100 cc , magnesium of 3 8 mg per 100 cc potassium of 31 9 mg per 100 cc and chloride of 1 374 mg per 100 cc Kling and Pincus[116] reported the gonococcal complement fixation test positive in 80 per cent of their cases of gonococcal arthritis while Myers Keefer and Holmes[137] found it positive in 67 per cent As in our series the results in the fluid corresponded with those in the blood in 42 of Myers 48 cases and in all but "a few per cent of Kling s cases The fluid was negative in 4 cases with positive blood doubtful in 1 case with negative blood and positive once with doubtful blood in Myers series Spink and Keefer[190] in a series of 70 patients found the complement fixation test positive in 47 of 54 bloods and in 21 of 35 joint fluids Myers Keefer and Holmes[137] cultured organisms from the fluid in 25 per cent of their cases Kling[116] in 33 per cent and Reitzel and Kohl[161] in 16 of 25 cases

### *Meningococcal Arthritis*

Involvement of one or more joints is not uncommon in meningococcemia As in other types of infectious arthritis, there is variation in the degree of joint involvement from arthralgia without objective findings through increasing degrees of swelling redness and tenderness to severe arthritis with red hot, tender, markedly swollen joints The effusions often persist for weeks, even though the septicemia and meningitis, if present, have been successfully treated by chemotherapy The residual joint damage varies with the severity of the arthritis but is, in general relatively less than that in other types of infectious arthritis

The 18 fluids in this series showed a wide range of variation corresponding to the degrees of severity From only 2 of them were organisms cultured, although cocci were seen in smears of 3 others The findings in the 2 positive fluids were essentially the same as those in the sterile group All the fluids were turbid, not very viscous and usually clotted Average total leukocyte count was 122,880 per cu mm , with an average of 93 per cent polymorphonuclears The fluid sugar averaged 60 mg per 100 cc compared with 108 mg in the serum The lactate concentration in 1 fluid was 21 mg per 100 cc compared with 23 mg in the serum

occur in either case, and they may, when untreated, last for months or years As a rule, only one joint is involved, it may be warm but usually not red or very tender

The fluids are turbid, not very viscous and usually do not clot The intra articular pressure in this series varied from 0 to 100 mm of fluid The total nucleated leukocyte counts ranged from 2,500 to 105,000 per cu mm, averaging 19,470, percentage of polymorphonuclears varied from 18 to 96, averaging 60 The total cell counts in 2 fluids from the 1 case in which the infection was limited to the synovial tissues were much lower than the average for the other fluids (5,150 and 6,800), and the percentages of polymorphonuclears were relatively low (42 and 53 per cent) There was apparently a slight tendency toward a predominance of lymphocytes in early cases in this series and an increase in polymorphonuclears in cases that had become chronic Analysis for sugar was made in 24 fluids The concentration in 4 of these was in the normal range, it was under 30 mg per 100 cc in 13 fluids, and sugar was entirely absent in 6 fluids The lactate content in 1 fluid was 79 mg per 100 cc compared with 16 mg in the serum The average concentration of albumin and globulin was 5 31 gm per 100 cc, and that of mucin was 0 044 gm nitrogen and 0 026 gm glucosamine per 100 cc—both essentially the same as in other fluids of Group II The average albumin/globulin ratio of 1 9 and viscosity of 7 7 at 38° C were also in the same range as others of Group II The mucin precipitated usually in a soft clump or shreds with cloudy solution

In all but 8 cases, the guinea pigs inoculated with fluids from this series of 29 cases showed evidence of tuberculosis Biopsies of synovial tissues were positive in the 13 cases in which they were performed In 4 of these cases, the guinea pig tests were negative Cultures were made on Dubos s medium[56, 70] in 5 fluids In 3 cases the results were the same as those of the guinea pig inoculations, in 1 the culture was positive with a negative guinea pig test and positive biopsy, and in 1 case the culture was negative with a positive guinea pig test

The findings in fluids from tuberculous arthritis resemble in general those in other types of infectious arthritis The variation from fluid to fluid is in accord with the varying degrees of joint involvement that occur

104 compared with 113 mg per 100 cc in the serum The total albumin and globulin concentration was low (3 13 gm per 100 cc ) with a relatively high globulin and an albumin/globulin ratio of 1 1 The mucin content was 0 069 gm nitrogen per 100 cc

In 10 cases of arthritis associated with bacillary dysentery, Labor and von Balogh[119] found agglutination titers ranging up to 1 200 in the fluid in a case in which the corresponding serum titer was 1 800 Zia and Smyly[112] reported agglutination titers for Flexner, Y and Shiga types of *B dysenteriae* of 1 320 1 160 and 1 80 in synovial fluid compared with 1 1 280 1 1,280 and 1 160 in the blood In 1 case, in which the Shiga bacillus had been cultured from the stools 3 weeks before joint aspiration the fluid showed no agglutination of the Shiga or Y bacilli but a 1 40 titer for the Flexner bacillus compared with respective titers in the blood of 1 80 1 80 and 1 40 [112]

### *Bacteroides Arthritis*

In bacteroides infections, involvement of joints occurs not uncommonly, and, as in other types of infectious arthritis varies from mild synovitis to severe purulent arthritis The degree of joint damage corresponds to the severity of the individual joint involvement

The 1 fluid of this type in the present series was grossly purulent and contained 530,000 leukocytes per cu mm , with 95 per cent polymorphonuclears Many gram negative bacilli were seen in the smear, and bacteroides were grown on culture

### *German Measles*

Arthralgia or synovitis with effusion occasionally occurs late in the course of German measles The effusions usually disappear in a few days without residual joint abnormalities

The 1 fluid of this kind in our series was slightly turbid and did not clot The total leukocyte count was 3,400 per cu mm with no polymorphonuclears The erythrocyte count was 1,000 The fluid sugar content was 85 mg per 100 cc compared with 117 mg in the serum The total albumin and globulin concentration was 1 6 gm per 100 cc Mucin nitrogen content was 0 129 gm per 100 cc , the viscosity at 38° C was 114 and the mucin precipitated well in a large, fairly tight clump in a clear solution

### *Tuberculous Arthritis*

The infection may be limited to the synovial tissues in tuberculous arthritis, though it usually also involves the bone Effusions

total nucleated cell counts and differentials with limits of 1,500 and 350,000 per cu mm Polymorphonuclears varied from 0 to 93 per cent lymphocytes from 5 to 65 per cent Dahl[104] found a pH between 7 15 and 7 45 in 33 of 41 fluids and a pH below 7 00 in only 1 fluid (pH 6 5) The protein content ranged from 3 0 to 5 5 per cent[104, 150] the viscosity from 5 6 to 24 0[115] and the sugar from 45 to 61 mg per 100 cc ' Scapini[178] in 1 case found a calcium content of 8 3 mg per 100 cc , phosphorus of 5 4 mg per 100 cc potassium of 23 1 mg per 100 cc and chloride of 980 mg per 100 cc Guinea pig inoculations were positive in only 78 per cent of Kling s cases

*Syphilitic Arthritis (Congenital)*

Effusions in congenital syphilis usually occur in the knees, but may involve other joints The joints are painless and not red, warm or tender The effusions may persist for years

The fluids show changes similar to, but less marked than, those of other Group II fluids They are usually turbid and not very viscous and may clot The total nucleated leukocyte count and percentage of polymorphonuclears in the 15 fluids of this series were relatively low, averaging 15,610 per cu mm and 46 per cent respectively The concentration of sugar was essentially the same as that in the serum The average lactate content in 2 fluids was 28 mg per 100 cc compared with 27 mg in the serum Average total albumin and globulin concentration (4 67 gm per 100 cc ), mucin content (0 058 gm nitrogen per 100 cc and 0 039 gm glucosamine per 100 cc ) and the viscosity of 11 at 38° C were the same as those of the majority of Group II fluids The mucin precipitated in a soft clump or shreds with cloudy solution in all but 2 fluids In 3 of the cases the Wassermann reaction was positive in the fluid, with a positive reaction in the blood in 2 cases, but a negative Wassermann with positive Hinton in the other case A fourth patient had a doubtful reaction in the fluid with a doubtful Hinton but positive Wassermann in the blood A fifth patient had negative Wassermann reactions in blood and fluid, but a positive Hinton in the blood

The findings in these fluids are in accord with an only moderately active infectious process

Synovial tissues in 1 case showed chronic and acute inflammation, with occasional neutrophils as well as lymphocytic and plasma cell infiltration Other features were synoviocytic hyperplasia and proliferation of subsynovial connective tissue

Histologically, in the synovial tissues Collins[30a] described tubercles in various stages of development The synovial membrane showed variation ranging from replacement by cellular granulation tissue, usually less vascular than other forms of granulation tissue, which was diffusely infiltrated by lymphocytes and plasma cells and contained only a few scattered giant cell systems" showing microscopic caseation and ill defined margins lost in the general cellularity of the tissue, to confluent tubercles with an obvious central mass of caseation Bennett[16a] mentions the occurrence of a thick surface layer of exudate

*Studies by Collins*[30a] *and Swift*[199] *of the relative accuracy of* biopsies of synovial tissue, guinea pig inoculations and cultures have indicated as is suggested by our results, that histological examination is the best single test to use in establishing the diagnosis Swift[199] found that the results of inoculation of 133 guinea pigs with synovial fluid or tissue from tuberculous joints agreed with the histological findings in 113 cases (85 per cent) Nine of the animals died too soon for diagnosis The tissue findings were positive and the guinea pig tests negative in 11 cases The guinea pig tests were, however, positive in 2 cases in which neither frozen nor paraffin sections showed evidence of tuberculosis

Blair and Hallman[18] found 34 positive cultures (by the method of Corper and Uyei[41]) out of 43 proved cases of tuberculosis, including 38 cases of bone and joint disease The guinea pig tests were positive in all of these, although a few of the animals which were killed in 2 weeks, showed evidence of tuberculosis only at the site of inoculation Of the 9 cases with negative cultures, 5 were positive on guinea pig inoculation and the other 4 were positive histologically They concluded that guinea pig inoculation is surer than culture and should be used if only one can be done

The findings in tuberculous arthritis are similar in general to those reported by others Widal and Ravaut[209] reported variations in the differential nucleated cell counts from an almost entirely lymphocytic formula in tuberculous synovitis of short duration to a polymorphonuclear picture in tuberculous arthritis of long duration Dopter and Tanton[54] in 2 cases Julliard[106] in 1 case Pewny[150] in 15 cases Keefer Myers and Holmes[104] in 5 cases McEwen[128] in 2 cases Kling[116] in 16 cases and Collins[30] report varying

infectious agent to the syndrome has not been obtained and it is possible that the syndrome may be related to rheumatoid arthritis In the present study, pleuropneumonia like organisms were cultured from the genito urinary tract of 9 of 16 patients with this syndrome and from synovial fluid from 2 patients

The 28 fluids of this kind in our series were turbid, not very viscous and usually clotted Findings varied with duration of effusion (Table III) The average total leukocyte count of 18,890 per cu mm, with 61 per cent polymorphonuclears, was in the same range as that of sterile fluids from gonococcal arthritis and of rheumatoid fluids The fluid sugar content (80 mg per 100 cc) was only slightly lower than that of the serum (91 mg) The lactate concentration in 1 fluid was 30 mg per 100 cc compared with 21 mg in the serum The total albumin and globulin content averaged slightly lower (4 49 gm per 100 cc) than that of other Group II fluids, and the globulin was relatively low The average mucin concentration was 0 067 gm nitrogen and 0 052 gm glucosamine per 100 cc, with an average relative viscosity of 11 at 38° C The mucin precipitated usually in a soft clump or shreds with cloudy solution

Patients with arthritis and genito urinary tract involvement (but without conjunctivitis), whose prostatic cultures were positive for pleuropneumonia like organisms, had essentially the same synovial fluid findings as patients with Reiter s syndrome

In summary, fluids from Reiter s syndrome resemble in most respects both those from rheumatoid arthritis and the sterile fluids from gonococcal arthritis

The histological findings in 7 biopsies were, as in the case of the fluid analyses, somewhat dependent on the duration and clinical course of the joint involvement [118a] Lesions 4 to 8 days old showed predominantly neutrophil infiltration and intense hyperemia with focal extravasation of red blood cells in the superficial synovialis In 2 to 3 week old lesions, cellular and fluid exudation were more extensive but lymphocytic infiltration and fixed cell proliferation tended to dominate the picture After 3 months, inflammation generally seemed to be subsiding In the case of 1 patient, however, in whom persistent synovial lesions of 15 months and 3½ years duration were biopsied, a chronic

The reports in the literature of the findings in fluids from syphilitic arthritis do not generally differentiate between congenital and acquired syphilis The cytological findings in the cases of congenital syphilis reported by Keefer[104] and McEwen and Thomas[120] showed more variation than our cases with total counts from 6 750 to 45 000 per cu mm and polymorphonuclears from 16 to 90 per cent We have not had any fluids from patients with acquired syphilis but Chesney Kemp and Baetjer[36] in 5 cases and Keefer Myers and Holmes[104] in 1 case found total counts from 4 500 to 24 000 per cu mm with polymorphonuclears from 24 to 88 per cent The fluid protein (including mucin) in Keefer Myers and Holmes case was 3 8 per cent. In Kling's[115] series the 18 cases of congenital and acquired syphilis cannot be separated completely In the acute effusions observed chiefly in congenital syphilis he found high cell counts (up to 23 000 per cu mm ) with predominance of polymorphonuclears (up to 93 per cent) but in chronic effusions the *lymphocytes predominated (up to 85 per cent)* The viscosities varied from 3 2 to 14 8 in his cases icteric index from 2 1 to 4 0 units The fluid cholesterol in 1 case was 83 mg per 100 cc compared with 161 mg in the blood

The relation between the fluid and blood Wassermann reactions in syphilitic arthritis has been the subject of considerable discussion In 4 cases of congenital syphilis reported by Reschke[163] the reactions were positive in both fluid and blood In his other 4 cases 1 of acquired syphilis and 3 in which the type of syphilis was not definite the fluid Wassermann was positive but the reaction in the blood was negative Keefer, Myers and Holmes[104] found positive Wassermann reactions in the blood in 4 cases, with positive reactions in 3 fluids and a doubtful reaction in 1 In Chesney Kemp and Baetjer's[36] cases of acquired syphilis and Kling's[111, 116] patients with acute and chronic syphilitic effusions the fluid Wassermann paralleled the blood reactions as in our cases Poehlmann[153] in a study of 100 fluids from syphilitics with and without joint symptoms never found a positive Wassermann in the fluid when the blood was negative as discussed above (see p 9) In 47 cases of untreated secondary syphilis the blood Wassermann was positive in 36 cases 25 of which had positive reactions in the fluid In 19 latent cases the blood Wassermann was positive in 12 cases 2 of which had positive fluid reactions In 9 tertiary cases all had positive blood Wassermanns and 3 had positive reactions in the fluid

## REITER'S SYNDROME

Joint involvement in Reiter's syndrome (non gonococcal urethritis, arthritis and conjunctivitis) resembles that in gonococcal and other types of infectious arthritis One or more joints may be involved with varying degrees of severity The effusions tend to persist longer than those of gonococcal arthritis often lasting many weeks or months Residual damage is less common than in gonococcal arthritis Clinically, this syndrome resembles infectious arthritis, but proof of the etiological relationship of any

grossly with clinical or laboratory evidence of the severity of the disease as a whole, with the degree of inflammation in the aspirated joint or the duration of the disease or the effusion Usually, the fluids showing the least variation from normal came from early, mild cases, though occasionally only slight abnormalities were found in effusions of many years duration The fluids ranged from clear to turbid Fifty-eight per cent of the present series clotted The intra articular pressure varied from 0 to 700+ mm of fluid The total nucleated cell count varied from 450 to 66,000 cells per cu mm * with an average of 15,310, while the percentage of polymorphonuclears ranged from 0 to 96, with an average of 65

The average concentration of sugar (65 mg per 100 cc ) was comparable to that in gonococcal arthritis, lower than that of Group I fluids, and higher than that of septic and tuberculous fluids The variation, however, was extremely wide, with limits of 0 and 132 mg per 100 cc The factors affecting the sugar level in these joints have been discussed (p 67) The concentration decreased with increasing inflammation, as shown in Figure 7, and with persistence of effusions (Table V) It showed relatively little relation to the total nucleated cell count It was regularly decreased in severe cases of long duration (Tables V and VII) and was temporarily low when the intra articular pressure was markedly elevated (Table XII) In 22 fluids the average lactate concentration was 31 mg per 100 cc in contrast to 22 mg in the sera

The average total albumin and globulin concentration in rheumatoid fluids was essentially the same as that in the other fluids of Group II, but, as in the case of the other findings, the variations were more marked than in Group I, as discussed above (p 39) Individual values varied from 3 30 gm per 100 cc , a concentration typical of non infectious fluids, to 8 89, the highest protein concentration found in any fluid of any kind It was the globulin fraction that was increased in the fluids with exceptionally high protein content In fact, the highest globulin concentrations in any fluids were found in rheumatoid effusions of long duration The globulin content of the fluid in such cases was essentially the same as that of the serum, although the fluid albumin content

*Since this study was completed 1 fluid with a leukocyte count of 116 200 has been obtained from a patient with rheumatoid arthritis

proliferative synovitis with lymphoid nodules indistinguishable from rheumatoid arthritis was present.[118a] (Synovial fluid was not obtained from these two joints.) Whether or not this was a chronic case of Reiter's syndrome or rheumatoid arthritis following Reiter's syndrome is unknown.

There are few reports in the literature on the findings in fluid from Reiter's syndrome. Quintin and White[154] noted that the fluid was cloudy and viscous and that there was a predominance of polymorphonuclear cells. Storm Mathiesen[194] reported that the number of cells varied. In 2 fluids he found an albumin content of 2.7 gm. per 100 cc. and globulin concentrations of 3.1 and 3.6 gm.

## RHEUMATOID ARTHRITIS

The fluids from cases presenting the characteristic features of rheumatoid arthritis—chronic, often symmetrical, joint involvement with thickening of synovial tissues, systemic involvement as indicated by fatigability, weight loss and an elevated sedimentation rate, and usually typical X-ray changes—have been studied as a group.* Separate analyses have, in addition, been made of the fluid findings in patients of this group who had generalized psoriasis, were under 12 years of age or had spondylitis (Marie-Strumpell type). The data from patients with ulcerative colitis associated with joint disease indistinguishable from rheumatoid arthritis have been kept separate. Cases with symptoms and signs suggesting rheumatoid arthritis but without adequate clinical, X-ray or histological evidence for a definite diagnosis, have been labelled rheumatoid arthritis—diagnosis probable.

Early proliferation and inflammation in synovial tissues are characteristic of rheumatoid arthritis and account for the frequency of joint effusions. It is not unusual for the effusions to last for years owing to persistence of low grade tissue changes. Only occasionally do the joints become red, hot or acutely tender, the usual joint symptoms being stiffness and aching pain of dull to moderate intensity.

Fluids from rheumatoid arthritis varied more than any other group in this study. In general, the variations could be correlated

*Since the permeability of synovial tissues to bacteria is increased in rheumatoid arthritis, a specific infectious arthritis is occasionally superimposed. In such cases the fluids are indistinguishable from those of infectious arthritis.

dylitis and peripheral joint involvement and 3 patients with psoriasis active at the time of aspiration showed no consistent variations from those in the whole group

The fluids from 45 cases of "rheumatoid arthritis—diagnosis probable" showed less marked changes than those from patients with characteristic rheumatoid arthritis (Figures 5, 6, 9, 10, 11, 12, 14 and the chart at the back of the book) In many fluids the abnormalities were only slightly greater than those of traumatic fluids However, in almost all cases at least one finding—the total leukocyte or polymorphonuclear count, the mucin precipitate, the viscosity, the sugar difference, or the protein or globulin concentration—showed a greater degree of change than is found in traumatic arthritis The findings in 2 patients with ulcerative colitis and joint disease consistent with rheumatoid arthritis were similar to those in rheumatoid patients

In patients receiving adrenocorticotrophic hormone or cortisone, the fluid abnormalities decrease In the majority of cases, the volume of fluid lessens, the total leukocyte and polymorphonuclear counts decrease, as from 30,800 to 150 cells per cu mm with 16 and 0 per cent polymorphonuclears respectively, the difference between serum and fluid sugar contents decreases, the type of mucin precipitate improves, and the relative viscosity of the fluid rises, in one instance from 13 to 6,080 at 38° C

The findings in fluids from rheumatoid arthritis reflect the variation in degree of synovial inflammation that can occur in this disease The alteration in mucin the increase in fluid globulin and the reduction in sugar level in the fluid with increasing severity are characteristic, though not specific

The most characteristic microscopic changes in the synovialis in our series correspond to those reported by Collins[39b] (1) hypertrophy of the synovialis and villi (2) hyperplasia of synoviocytes, (3) massive lymphocytic and, at times, plasma cell infiltration of the subintima with large focal collections in the villi, (4) inflammatory hyperemia and edema varying in degree In addition there may be patchy fibrinoid change or fibrin deposition, frequently in association with necrobiosis and collagen alteration, some neutrophil infiltration, focal red-blood cell extravasation and occasionally, an increase in faintly staining hematoxylino-

remained approximately two thirds of the serum content The maximal concentration of globulin in any other type of fluid was 3 1 gm per 100 cc, while 7 rheumatoid fluids out of 58 had concentrations above 3 0 gm, 1 being 6 77 gm per 100 cc The average albumin/globulin ratio (1 5) was slightly lower than that of other Group II fluids, and the minimal ratio (0 31) was much lower than that found in any other type of fluid

The electrophoretic patterns of fluids in rheumatoid arthritis gave further evidence of the variations in protein fractions [168 169] In early or mild cases and occasionally in moderately severe cases, the pattern resembled that of traumatic fluids, with the albumin higher than in the serum, the alpha-1 and beta globulins essentially the same as in the serum and the alpha 2 and gamma globulins lower than in the serum In the majority of cases of longer duration or greater severity, the albumin in the fluid was equal to or lower than that of the serum, whereas the gamma globulin was higher in the fluid In a few patients who had had effusions of years duration with relatively little objective evidence of joint damage, the electrophoretic pattern disclosed marked elevation of the gamma-globulin in the fluid above that in the serum

The average concentration of mucin was the same as that for other Group II fluids, but here again the range was greater, extending from a trace to 0 166 gm nitrogen and from 0 006 to 0 081 gm glucosamine per 100 cc Considerable variation in precipitability of mucin was found also, although in the majority of rheumatoid fluids a poor precipitate—either a soft, friable mass with cloudy solution or just a flocculent precipitate—was obtained with acetic acid Only occasional early or mild cases had good ropy mucin precipitates with clear surrounding solutions (see Figure 13a) The viscosity of the fluids varied from 2 8 to 59, with an average of 11 at 38° C

The pH varied from 7 11 to 7 42 with an average of 7 22 compared with an average of 7 45 in the serum The difference between fluid and serum tended to increase in severe cases The freezing point depressions in 2 cases were — 542° and — 551° C, compared with — 562° and — 606° in the sera

Our findings in the fluids from 10 children under 12 (2 of whom presented the picture of Still s disease ) 10 patients with spon

with rheumatoid arthritis both before and after synovectomy The patients had typical rheumatoid arthritis of 3½ and 2 years' duration with involvement of many joints and marked constitutional symptoms In the first case no effusion recurred in the knee postoperatively, but 1 5 cc of fluid were withdrawn 2 years later Following this aspiration, a small effusion developed, 10 cc of fluid were withdrawn at that time and 15 cc 4 months later In the second case, a slight effusion recurred about 6 months after operation and persisted Twenty-five cc of fluid were aspirated 3 years after synovectomy In both cases the fluid findings were fundamentally the same preoperatively and postoperatively with the exception of the mucin content (see Table XIV)

In Case 1, the unoperated knee was involved throughout the period of study and served as a basis of comparison Three years after synovectomy the fluid from the operated knee was the same as that withdrawn simultaneously from the unoperated knee, with these exceptions the mucin nitrogen and glucosamine contents from the operated knee were only 0 01 and 0 006 gm per 100 cc, the relative viscosity was 5 1 and the mucin precipitated as a few shreds in a cloudy solution, whereas the fluid from the unoperated knee contained 0 09 gm of mucin nitrogen and 0 067 gm of mucin glucosamine and had a viscosity of 25, and the mucin precipitated well in a soft clump The patient had developed amyloidosis with renal involvement 1 year after operation with subsequent reduction in the protein content of the serum There was a corresponding decrease in the protein concentration in the synovial fluids, but the albumin/globulin ratio remained in the same range as that of the serum and was identical in both fluids The fluid sugar, which was markedly reduced preoperatively, remained essentially the same after synovectomy This finding is in accord with the hypothesis that the reduction of sugar in rheumatoid joints is due more to decreased entrance than to increased utilization (see p 67)

In Case 2 the concentrations of albumin, globulin and sugar remained unchanged after synovectomy, but as in the first case, the mucin nitrogen was reduced from 0 09 gm to just a trace The great decrease in mucin in both cases suggests that the tissue removed at operation may have been active in the formation of the synovial mucin and gives further evidence in favor of the

philic ground substance * Such changes seem to indicate a more *intense inflammatory activity and are particularly common in the* early or rapidly progressing stages of the lesions [118a]

The cytological variations found in this series of rheumatoid fluids correspond closely with those reported by Fischer[96] in 9 cases Keefer Myers and Holmes[106] in 16 cases McEwen[108] in 8 cases Collins[98, 99] in 31 cases Jordan[107] in 5 cases and Burman and Kling[97] in 2 cases The total nucleated cells in their fluids ranged from 1 700 to 74 800 per cu mm percentages of polymorphonuclears from 3 to 100 Kling[115] on the other hand reported variations from 400 to 230 000 cells with polymorphonuclears of 8 to 94 per cent in 34 cases The volume of fluid obtained by Collins and Kling varied from 3 to 160 cc the viscosity from 3 0 to 32 In 2 fluids Ragan and Meyer[138] found a variation in relative viscosity from 4 5 to more than 1 100 *The extremely high value was estimated by extrapolation using the figure* obtained after diluting the fluid with 0 85 per cent saline Chemical studies were made by Fischer[96] Keefer Myers and Holmes[104] Collins[98] Jordan[100] Kling[115] Ragan and Meyer[138] and Sundblad[134] The protein contents (presumably including mucin) varied from 2 4 to 8 6 per cent the sugar from 17 to 145 mg per 100 cc uric acid from 2 2 to 4 7 mg per 100 cc phosphate from 3 1 to 4 3 mg per 100 cc calcium from 5 3 to 11 6 mg per 100 cc pH from 7 27 to 7 6 Fischer[96] reported 1 mucin of 0 41 per cent, 1 globulin of 3 95 per cent and a surprisingly low albumin value 0 32 per cent Olhagen[141a] reported remarkably high concentrations of gamma globulin in fluids from patients with rheumatoid arthritis of long duration Ragan and Meyer[138] in 41 fluids found variations in concentration of hyaluronic acid from 0 08 to 0 63 mg per cc and Sundblad[134] in 37 fluids found an average of 0 150 gm per 100 cc Burman and Kling[97] reported that Evans blue entered the involved joints in patients with rheumatoid arthritis and concluded that the more acute the arthritis the greater the entrance of dye

The findings in the groups studied separately by McEwen[108] and Kling[115] *also correspond with those in rheumatoid arthritis in general* Their series of 5 and 24 cases designated as infectious arthritis presumably represent acute and somewhat atypical cases of rheumatoid arthritis The total cell counts varied from 1 500 to 80 000 per cu mm with 35 to 95 per cent polymorphonuclears The icteric index varied from 2 to 5 units except in 1 fluid which showed 12 Viscosity ranged from 2 8 to 24 0 and calcium from 8 1 to 9 7 mg per 100 cc

### *Effect of Synovectomy on Synovial Fluid Findings in Rheumatoid Arthritis*

Synovial fluid was obtained from the knee joints of 2 patients

*The tinctorial properties of this substance with regard to metachromatic dyes as well as aniline blue and hematoxylin seem to correspond with those of synovia *but as yet no connection between its interstitial accumulation and changes in* synovial fluid has been found

and After Synovectomy

| Globulin gm per 100 cc | | | A/G ratio | | | Mucin nitrogen gm per 100 cc. fluid | | Mucin glucosamine gm per 100 cc | | Viscosity at 38 C | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Serum | Fluid L | Fluid R | Serum | Fluid L | Fluid R | L | R | L | R | L | R |
| 3 45 | 1 86 | 1 98 | 1 05 | 1 35 | 1 30 | 087 | 039 | | | | |
| 4 16 | | 2 55 | 0 94 | | 0 98 | | 046 | | | | |
| 3 26 | 1 96 | | 0 83 | 0 73 | | 082 | | 067 | | 23 1 | |
| 3 54 | | 1 69 | 0 61 | | 0 57 | | 012 | | 006 | | 6 3 |
| 2 83 | 1 44 | 1 24 | 0 72 | 0 54 | 0 58 | 091 | 008 | 067 | | 25 3 | 5 1 |
| 2 47 | 2.25 | | 2 09 | 1 27 | | 076 | | | | | |
| 3 35 | 3 23 | | 1 25 | 0 93 | | 092 | | | | 9 4 | |
| 3 09 | 2 68 | | 1 42 | 1 13 | | Trace | | 025 | | 5 7 | |

those in mild cases of rheumatoid arthritis The fluids were fairly clear and usually did not clot The intra articular pressure varied from 0 to 200 mm of fluid The total nucleated cell counts and percentage of polymorphonuclears were lower than in most rheumatoid fluids, ranging from 635 to 6 200 per cu mm and from 0 to 60 respectively The fluid cytological changes during and following a typical attack in the patient who had had intermittent effusions for 20 years are shown in Figure 8 In the other patient, there was an initial rise in percentage of polymorphonuclears followed by a rise in mononuclears and lymphocytes (Table III) The concentration of sugar in the fluids was essentially the same as that in the serum The total contents of albumin and globulin and the albumin/globulin ratios in the fluids from both patients were the same as the average for rheumatoid fluids The mucin concentration (0 050 gm nitrogen per 100 cc ) was slightly lower than the average in rheumatoid fluids but the mucin precipitate was usually a tight ropy clump with clear solution The relative viscosity tended to be low during the first day or two of the effusion (4 10) and to increase later (up to 25) The pH value in 1 fluid was 7 66 as compared with 7 54 in the serum

Krummel[11] and Collins[30] also found low total cell counts in fluid from intermittent hydrarthrosis although Collins noted high percentages of polymorphonuclear cells Krummel in the case of a patient who had bilateral knee effusions recurring at 10 and 12 day intervals found that polymorphonuclears and mononuclears increased with increasing effusion lymphocytes

TABLE XIV Synovial Fluid Findings in Two Patients with Rheumatoid Arthritis Before

| Case no and date | Amount cc fluid | | Leukocytes per cu mm fluid | | Polymorphonuclears per cent fluid | | Sugar mg per 100 cc | | | Protein gm per 100 cc | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | Serum | Fluid | | Serum | Fluid | |
| | L | R | L | R | L | R | | L | R | | L | R |
| Case 1 | | | | | | | | | | | | |
| 11/27/35 | 18 | 50 | 66 000 | 40 000 | 93 | 92 | 100 | 22 | 13 | 7 06 | 4 37 | 4 55 |
| 1/18/37 | 20 | 50 | | 41 000 | | 89 | 100 | | 0 | 8 05 | | 5 04 |
| 8/13/37* | | | | | | | | | | | | |
| 11/24/39 | 90 | 1 5 | 8 450 | 17 050 | 66 | 68 | 83 | 4 | 8 | 5 98 | 3 40 | |
| 1/30/40 | 110 | 10 | 6 100 | 18 650 | 31 | 81 | | | | 5 72 | | 2 66 |
| 5/15/40 | 70 | 7 | 4 300 | 7 550 | 63 | 78 | 81 | 10 | 5 | 4 87 | 2 21 | 1 95 |
| Case 2 | | | | | | | | | | | | |
| 1/ 2/36 | 70 | | 21 700 | | 67 | | 99 | 94 | | 7 63 | 5 12 | |
| 6/15/37† | 30 | | 29 800 | | 90 | | 100 | 64 | | 7 54 | 6 24 | |
| 5/28/40 | 25 | | 10 050 | | 62 | | | 67 | | 7 43 | 5 70 | |

*Synovectomy right knee
†Synovectomy left knee

theory that mucin is formed by the connective tissue cells around the joint[17, 79, 131] On the basis of experimental work (see review[17]) it may be assumed that the connective tissue lining of the joint is re formed but apparently the new cells in these 2 cases were not capable of producing mucin in large quantities

## INTERMITTENT HYDRARTHROSIS

Idiopathic intermittent hydrarthrosis is characterized by periodic joint effusions recurring at regular intervals with great precision The cause of this phenomenon and the factors controlling the amazing regularity of the recurrences are not known In rheumatoid arthritis effusions occasionally recur with similar regularity, and it seems possible that many if not all, patients with intermittent hydrarthrosis have atypical rheumatoid arthritis We have seen only 2 cases in which we originally made a diagnosis of idiopathic intermittent hydrarthrosis In 1 of these however, the development of persistent synovial thickening of both knees, X-ray evidence of atrophy of the surrounding bones and an elevation of the sedimentation rate have made it apparent that the patient has rheumatoid arthritis, even the other patient, who had intermittent effusions for 20 years, finally developed an elevated sedimentation rate and synovial thickening of one knee that persisted between attacks

The fluid findings in these 2 cases were alike and resembled

The findings in bursal fluids suggest that the equilibrium between bursa and blood differs from that between joint and blood The low concentration of sugar in bursal effusions of short duration, in the absence of bacteria or marked leukocytosis, would be unusual in synovial fluid The variation in the concentrations of albumin, globulin and mucin is greater than that found in comparable joint fluids In fluids from 3 so called ganglions, no precipitate was obtained with acetic acid until serum was added Apparently the polysaccharide was present without adequate protein to allow precipitation of mucin

increased when the effusion was subsiding Dopter and Tanton[44] reported 50 per cent polymorphonuclears and 50 per cent lymphocytes in 1 case and 100 per cent lymphocytes in another case The viscosity in 1 fluid studied by Ragan[155] was 11 2 The so called albumin content of fluids in Krummel s series determined refractometrically ranged from 5 29 to 6 5 per cent The pH of 1 fluid reported by Krummel was 7 5 and of 1 recorded by Coppo and Levi[40] was 7 8 Scapini[175] in 1 case reported a calcium content of 8 7 mg per 100 cc phosphorus of 3 8 mg per 100 cc, magnesium of 2 35 mg per 100 cc potassium of 21 2 mg per 100 cc and chloride of 672 mg per 100 cc

BURSITIS AND BAKER S CYSTS

Acute and chronic inflammation of bursae may be associated with various joint diseases such as rheumatoid arthritis, may be of known infectious origin, or may be of unknown etiology and unassociated with involvement of other skeletal tissues The term Baker s cyst has been used to designate synovial lined cysts that are presumed to have been in communication with joints and sub sequently sealed off The present series includes 7 cases of acute bursitis of less than 6 weeks duration, 4 cases of chronic bursitis, 5 cases of so called Baker s cysts and 4 cases of walled off cysts in popliteal space or quadriceps pouch in patients with rheumatoid arthritis

Fluids from all types of bursitis and Baker s cysts show wide variations in cytological and chemical characteristics As a result, fluid examination is not usually of value in determining the type or even duration of the bursitis However, in our series high total leukocyte counts (10 000 to 50,000 per cu mm ) and a high percentage of polymorphonuclears (60 to 90) were found only in some cases of acute bursitis and in some of the cysts in patients with rheumatoid arthritis In all other cases the leukocyte counts ranged from 500 to 1,000, with 0 30 per cent polymorphonuclears

The majority of all of the fluids were turbid and slightly blood tinged and either did not clot or formed only small, friable clots The concentrations of sugar were usually low, ranging from 0 to 95 mg per 100 cc, with an average of 40 The total albumin and globulin contents were relatively high, ranging from 1 9 to 8 1 gm per 100 cc, with an average of 5 2 The mucin nitrogen concentration tended to be high averaging 0 071 gm per 100 cc, with a range from 0 to 0 20 In 1 case of chronic inflammation of a subacromial bursa, in which calcium was shown by X ray, the calcium content was 13 9 mg per 100 cc (see p 87)

a reduction of viscosity per unit concentration (Figures 12 and 13)

It is apparent that analysis of joint fluid aids materially in distinguishing the two large groups of joint diseases While no single finding is absolutely conclusive, any of the conditions listed in Group I is fairly definitely ruled out by aspiration of a fluid which is turbid, clots, has a low viscosity, and shows a small amount of flocculent mucin precipitate, a total albumin and globulin concentration of more than 5 0 gm per 100 cc , a difference in fasting sugar content between serum and fluid of more than 30 mg per 100 cc , a total nucleated cell count of over 5,000 per cu mm and an absolute polymorphonuclear count of over 1,000

For differentiation between individual fluids within either of the two large groups, synovial fluid examination is of less value There are, however, certain findings that give suggestive evidence in favor of one or another diagnosis In disseminated lupus erythematosus, for instance, in contrast to rheumatoid arthritis, polymorphonuclears have never been above 260 per cu mm (Figure 6), the concentration of mucin nitrogen and glucosamine has almost always been high (Figure 11), the mucin precipitate has always been good (a ropy clump in a clear solution) and the relative viscosity of the fluid has been high (Figure 12 and the chart at the back of the book) Similarly, in rheumatic fever the concentration of mucin is relatively high (Figure 11), the mucin precipitate usually good and never poor, and the viscosity relatively high (Figure 12) As a result, in a patient in whom the differential diagnosis is between rheumatic fever and rheumatoid arthritis, the finding of a low concentration of mucin with poor precipitate and low viscosity would give evidence in favor of a diagnosis of rheumatoid arthritis rather than rheumatic fever The extremely high concentration of mucin (Figure 11) and high relative viscosity (Figure 12) usually found in fluids from osteochondromatosis aid in differentiation from traumatic arthritis Aspiration of hemorrhagic fluid especially if it contains free fat in the absence of severe acute trauma or hemophilia (and in the presence of a persistent, usually painless effusion), suggests the diagnosis of hemorrhagic villous synovitis There is one combination of findings that is of considerable diagnostic value namely, in a fluid of relatively short duration (weeks or

# VI

## *Diagnostic Value of Joint Aspiration*

FROM a survey of the findings in the joint diseases studied, it is clear that the information gained from certain analyses is of value in diagnosis and prognosis The significant findings are shown in the chart at the back of the book They can be roughly summarized as follows Fairly clear, viscous fluids that do not clot are found usually in traumatic arthritis, osteochondritis dissecans osteochondromatosis Charcot joints and degenerative joint disease, occasionally in tumors, in rheumatic fever and in mild atypical cases of rheumatoid arthritis The majority of rheumatoid fluids and all specific infectious fluids are turbid and less viscous than Group I fluids and often clot There are other important differences between the two main groups The total nucleated cell count is usually below 3,000 per cu mm, with absolute polymorphonuclears less than 500 in Group I fluids and above 3 000 with more than 500 polymorphonuclears in Group II fluids (Figures 5 and 6) The sugar content is approximately the same as that of the blood in Group I fluids, is slightly lowered in the majority of Group II fluids varies from no sugar to a normal value in rheumatoid fluids and is low or absent in infected fluids with positive cultures and in most tuberculous fluids (Figure 14) The total concentration of albumin and globulin is usually below 5 0 gm per 100 cc, with an albumin/globulin ratio above 2 0 in Group I fluids and above 4 0 gm per 100 cc, with an albumin/globulin ratio below 2 0 in Group II fluids (Figure 9) The concentration of mucin is usually normal or elevated in Group I fluids, while in Group II the concentration is often lowered and there is associated loss of the characteristic precipitability and

count showed 9 per cent polymorphonuclears, 29 per cent lymphocytes and 62 per cent monocytes The mucin precipitated very well in a large ropy clump with clear solution The hemorrhagic fluid with low leukocyte count was consistent with a diagnosis of hemorrhagic villous synovitis The patient did not return as requested but 10 months later he was admitted to the hospital because of persistence of the effusion in the left knee Examination was unchanged Hemorrhagic fluid was again obtained with 363 000 erythrocytes per cu mm The leukocyte count was 3 750 with 60 per cent polymorphonuclears The mucin precipitated very well On the basis of the persistent painless effusion, found on aspiration to be bloody and to have a relatively low leukocyte count and good mucin, a diagnosis of hemorrhagic villous synovitis was made At operation the synovial tissues were greatly thickened and bronze in color The histological appearance was consistent with "pigmented villo-nodular synovitis

*Case 3* An 18 year old white boy was admitted with a complaint of pain and swelling in the left knee of 5 months duration A cyst of the internal semilunar cartilage of the left knee had been removed 21 months before admission The knee had remained absolutely symptom free until 5 months before admission when he was thrown against an anchor bar on a ship during a storm striking the left knee The knee had been swollen and painful since that time The past history was non contributory Examination showed effusion in the left knee with tenderness over the anterior aspect of the medial condyle the internal lateral ligament and the posterolateral aspect of the lateral meniscus The joint capsule was markedly thickened A diagnosis of traumatic synovitis was made and synovectomy and removal of the external semilunar cartilage were performed Frozen sections of the synovialis were not made because the diagnosis was thought definite The fluid obtained at operation had a total count of 5 250 per cu mm with 58 per cent polymorphonuclears a protein content of 5 38 gm per 100 cc , and no sugar All these findings were inconsistent with those of traumatic fluids and gave the first indication that the diagnosis was incorrect The combination of relatively low total leukocyte and polymorphonuclear counts with a low sugar concentration in an effusion of only a few months duration was strong evidence in favor of tuberculous arthritis Histological examination of the synovialis confirmed this diagnosis and the knee was subsequently fused In this case preoperative examination of the fluid would have suggested the correct diagnosis which could have been confirmed by examination of frozen sections of synovialis at the first operation and a second operation would have been avoided

*Case 4* A 23 year old woman was admitted with the complaint of swelling and limitation of motion of the left knee One year before admission she had squatted to pick up an object and her left knee had locked It had become swollen and stiff returning to normal slowly Four months before admission the swelling had reappeared and persisted A diagnosis of internal derangement of the knee was made and the internal semilunar cartilage was

a few months), the combination of a relatively low leukocyte count (25,000 cells per cu mm or below) and polymorpho nuclears of 50 per cent or less with a low content of sugar (20 mg per 100 cc or below) is, we think, strongly suggestive of tuberculosis

Although the findings in any individual fluid within either one of the groups are not diagnostic, when combined with the clinical and other laboratory data they may be of definite value in differential diagnosis As a few typical examples will show, early synovial fluid study may aid in confirming a diagnosis suggested clinically (Cases 1 and 2 following), it may, by facilitating diagnosis, remove the need for operation (Cases 3 and 4) or direct treatment toward the underlying cause of the disease (Case 5) In other cases, clinical corroboration of a diagnosis indicated by the fluid analysis may not be obtained for some time (Case 6)

*Case 1* A 30 year old tractor driver was admitted with the complaint of pain in the left knee of 1 year s duration One year before admission he had fallen against a roll of paper cutting the left lower shin Very gradually pain had developed in the left knee Subsequently the knee had become swollen tender and hot Following aspiration of fluid 5 months before admission the symptoms had subsided but the pain and swelling had recurred 1 month later Examination showed swelling of the left knee with pain on motion and slight tenderness over the anteromedial aspect Roentgenograms showed extensive calcification in the knee joint The diagnoses suggested clinically were osteochondromatosis or internal derangement of the knee joint The synovial fluid was slightly cloudy did not clot and contained 1 050 leukocytes per cu mm with 1 per cent polymorphonuclears The fluid sugar was 93 mg per 100 cc compared with a serum sugar of 101 mg The relative viscosity was 147 the mucin 09 gm nitrogen per 100 cc the albumin and globulin 3 0 gm per 100 cc and the albumin/globulin ratio 3 0 The mucin precipitated well in a ropy clump with clear solution The very high viscosity and high mucin concentration in this fluid differentiated it from those usually found in internal derangement of the knee The fluid was consistent with osteochondromatosis Subsequent synovectomy corroborated the diagnosis

*Case 2* A 19 year old boy was seen in the emergency ward because of swelling of the left knee of 3 years duration The onset of swelling had been insidious There had been no pain in the knee and no other joint symptoms Hemorrhagic fluid had been aspirated on two occasions Examination showed a moderate sized effusion in the left knee Roentgenograms showed no bony abnormalities On aspiration of the knee bloody fluid containing 550 leukocytes and 391 000 erythrocytes per cu mm was obtained The differential

cartilages was performed. At operation the synovial tissues showed marked thickening and after histologic examination a diagnosis of chronic synovitis was made The synovial fluid aspirated preoperatively, had a total nucleated count of 17,800 per cu mm, with 96 per cent polymorphonuclears Our present knowledge of the significance of fluid findings would have told us that such changes do not result from trauma but this was not recognized at that time When the patient was seen 8 years after operation she had malaise persistence of slight swelling and pain on motion in the right knee pain in the right shoulder left hand and left wrist and a corrected sedimentation rate of 1 02 mm per minute A diagnosis of rheumatoid arthritis was made Re-examination of the original biopsy specimen, by a pathologist versed in the study of synovial tissues showed changes interpreted as consistent with rheumatoid arthritis

removed The synovial membrane was found to be thickened and there was definite pannus formation in the region of the intercondylar notch Fluid removed at the time of operation contained 25 600 leukocytes per cu mm, with 96 per cent polymorphonuclears and 41 mg of sugar per 100 cc—findings entirely inconsistent with those of traumatic fluid Three months later the patient s left ankle became swollen and during the following month the right hip knee and ankle became involved If synovial fluid had been obtained on admission, it would have suggested the correct diagnosis of rheumatoid arthritis

*Case 5* A 45 year old man was admitted because of a cough present for 3 weeks that was productive of large amounts of white sputum Two months before admission he had had his teeth extracted for treatment of "arthritis which he had had for 1½ years The joint symptoms had begun with stiffness of knees ankles wrists and right elbow and enlargement of the terminal phalangeal joints of the fingers There had been gradual progression of the involvement of knees and ankles with marked pain and swelling Examination on admission showed diminished breath sounds over the left upper chest and a roentgenogram disclosed an area of increased density in the left upper lobe There was marked clubbing of all fingers and toes The knees and ankles were swollen and very tender Synovial fluid aspirated from the left knee was slightly cloudy and clotted firmly The leukocyte count was 100 per cu mm with 20 per cent polymorphonuclears and 80 per cent lymphocytes The fluid protein content was 2 2 gm per 100 cc The mucin precipitated in small flecks in a slightly cloudy solution Further study of the pulmonary lesion suggested that it was a neoplasm and pneumonectomy was performed A tumor involving most of the left upper lobe was found and the histological diagnosis was adenocarcinoma Grade II The immediate postoperative course was uncomplicated except for slowly increasing dyspnea relieved by thoracentesis However on the twentieth postoperative day respirations suddenly became irregular and ceased

The combination of synovial fluid findings—the low cell count with few polymorphonuclears and the slight elevation of protein combined with the relatively high fibrinogen content (as indicated by the large firm clot)—would be most unusual in rheumatoid effusions of months duration They are very suggestive of pulmonary osteoarthropathy and could if obtained earlier have aided in recognition and treatment of the underlying disease

*Case 6* A woman of 49 was admitted with the complaint of pain and swelling of the right knee of 3 years duration The symptoms had begun immediately after injury to the knee by a fall from a bus and had persisted to the time of admission There had been frequent episodes of 'locking during the year before entry No other joint involvement or associated constitutional symptoms were elicited Examination showed marked effusion in the knee with tenderness over the external tibiofemoral fossa and increased lateral mobility A diagnosis of internal derangement of the knee was made and synovectomy with removal of both external and internal semilunar

diffusible, non utilizable substances in the joint, the entrance of glucose is slow. The delay in appearance, present even in normal joints, is enhanced with increasing inflammation. In mild cases, as in traumatic arthritis, the rate of entrance apparently remains almost equal to the rate of utilization or removal and equilibrium is maintained with a fluid concentration nearly equal to that of the blood. In severe inflammation, as in severe rheumatoid arthritis or infectious arthritis, the entrance is decreased so that, with increased consumption, the fluid sugar concentration is markedly lowered. The mechanism of this differential entrance of proteins and sugar is not understood, but the results emphasize that a variety of factors is involved in transfer across the synovial tissues.

Alterations in the synovial tissues lead also to diminished removal of colloidal and particulate matter. Experimental evidence suggests that this is due to a decreased number of synovial lymphatics (see review[12]). The reduced absorption, combined with greater entrance, probably accounts for the increasing protein concentration and decreasing albumin/globulin ratio in rheumatoid effusions of long duration. Whether or not local production of one or more protein fractions also plays a role is not known. The abnormally high concentration of colloidal material raises the osmotic pressure and presumably leads to persistence of the effusion.

The altered metabolism of the joint in disease is apparent in the case of sugar and mucin and tends to increase with severity of inflammation. Greater utilization of sugar results from various factors: increased activity of fixed tissue cells, a larger number of leukocytes in the synovial fluid, and bacteria, if present. Greater metabolic requirement for sugar, coupled with decreased supply, may lower the fluid sugar to a level which may impair nutrition of cartilage. In the case of mucin both formation and destruction may be affected. In traumatic effusions the unit concentration of mucin remains normal despite a great increase in fluid volume. Trauma seemingly stimulates formation of mucin by the connective tissue cells and does not lead to an increase in the rate of mucin destruction. Infectious and many rheumatoid fluids, on the other hand, show a decreased concentration of mucin, a reduced viscosity and a soft or flocculent precipitate with acetic acid. The similarity of these changes to those produced by enzymatic di-

# VII

## *Physiological Considerations*

A SURVEY of the findings in effusions from various joint diseases corroborates the hypothesis that joint fluid reflects changes produced in synovial tissue by disease There are two fundamental alterations an abnormality in the exchange of substances between the blood or lymph and the joint and a disturbance of intra articular metabolism

The degree of permeability of the blood joint barrier varies with the degree and type of synovial inflammation The difference is not apparent in the case of diffusible non utilizable substances whose distribution in joint disease follows the laws that apply to normal joints There is, of course increased entrance of such substances associated with the increase in amount of fluid entering the joint, but equilibrium is maintained The difference between types of joint disease becomes apparent in the variation in the increase in number of cells and in the permeability to bacteria and proteins including fibrinogen and presumably anti bodies and enzymes The minimal inflammatory reaction produced by trauma causes only slight increase in leukocytes, albumin, globulin and fibrinogen and the ratio of albumin to globulin in the fluid remains high In rheumatoid and in infectious arthritis there is greater entrance of these substances and, with the exception of leukocytes in rheumatoid arthritis, a progressive rise with increasing severity of the disease With the increased entrance of protein the differential permeability decreases globulins enter the joint more readily and the albumin/globulin ratio of the fluid more closely approaches that of the serum In contrast to the rapid increase in number of cells and amount of proteins and

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gestion of mucin suggests that increased destruction of mucin takes place in these joints, though incomplete synthesis may explain, at least in part, the reduction in viscosity and altered precipitability of mucin Attempts to demonstrate the presence of hyaluronidase in normal or pathological fluids have not been successful

The relation of synovial fluid findings to the degree of inflammation in the synovialis can be used to differentiate non traumatic joint diseases from traumatic arthritis of any type Within the two large groups, further differentiation may be possible because of the specific combination of fluid abnormalities produced by some individual diseases

In all cases in which both synovial fluid and biopsied synovial tissue were available, an attempt was made to correlate the degree of abnormality in the fluid with that in the synovialis Exact correlation was not possible but in all diseases the grade of reaction found in the tissues was usually of the same order as that of the fluid In the 2 cases of degenerative joint disease, for instance, in which the synovial tissues showed the most marked inflammation, the total proteins, especially the globulin fractions, were highest and the mucin content lowest

Synovial fluid thus presents itself as a reflection of tissue inflammation that may be of value in diagnosis and as a tool for further study of the physiology of articular tissues and the blood tissue barrier

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